SPECIAL ISSUE: NOVEL THERAPIES, DIABETES, AND CARDIOVASCULAR OUTCOMES

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Evidence-Based DIABETES MANAGEMENT™

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People with diabetes should check their feet daily.

CELLULAR TISSUE PRODUCTS
The American Diabetes Association recently offered a comprehensive overview of approaches to treating diabetic foot ulcers, which featured cellular tissue products. Although these products require higher up-front costs, they can lead to significant long-term benefits and savings, SP607.

RAISING AWARENESS
Foluso A. Fakorede, MD, a cardiologist practicing in the Mississippi Delta, writes about the need to raise awareness of coronary atherosclerosis disease and peripheral atherosclerosis disease. Dr Fakorede seeks to reduce unnecessary amputations among patients who have lived for many years with diabetes, SP609.

THERAPIES IN GUIDELINES, PATHWAY
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INTERVIEW

Time for a "New Goalpost" in Cardiovascular Outcomes Trials, Kosiborod Suggests

Mary Caffrey

IN A JULY EDITORIAL in *Circulation,* Mikhail Kosiborod, MD, FACC, FAHA, and coauthor Michael E. Nassif, MD, issued a call to their fellow cardiologists: The specialty is "well-poised to take the lead" in using newer classes of therapies that can lower cardiovascular risk among patients with type 2 diabetes (T2D).[1]

In November, Kosiborod was a coauthor on a much-anticipated consensus pathway from the American College of Cardiology (ACC) on treating patients with both T2D and atherosclerotic cardiovascular disease.[2] The pathway outlined how cardiologists should use newer agents—specifically, sodium glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists—with the goal of preventing heart attacks, strokes, heart failure hospitalizations and/or early cardiovascular death.

A decade ago, this would have been difficult to fathom, Kosiborod said in an interview with *Evidence-Based Diabetes Management*™ (*EBDM*). The concept of what can be done for T2D patients with medication has undergone a revolution, thanks to the 2008 FDA guidance[3] that launched a new staple of annual meetings for the ACC, the American Heart Association, the American Diabetes Association (ADA), and the European Association for the Study of Diabetes (EASD): the dedicated cardiovascular outcomes trial (CVOT).

Since the FDA began requiring cardiovascular outcomes trials for new glucose-lowering therapies, there has been a paradigm shift in the expectations for what can be achieved with medication in diabetes care.

CONTINUED ON SP602

REGULATORY UPDATE

After FDA Panel Vote, Some See "Next Generation" of Cardiovascular Safety Trials for Diabetes Drugs

Mary Caffrey

LARGE CARDIOVASCULAR OUTCOMES TRIALS (CVOTs), which began a decade ago, will likely remain part of the drug approval process for companies that develop treatments for type 2 diabetes (T2D). But based on a 2-day hearing and the October 25, 2018, vote of an FDA panel, changes to the trials seem likely.

The question to the FDA's Endocrinologic and Metabolic Drugs Advisory Committee was "Should an unacceptable increase in cardiovascular risk be excluded for all new drugs to improve glycemic control in patients with type 2 diabetes, regardless of the presence or absence of a signal for cardiovascular risk in the development program?" Panelists voted 10-9 to keep the trials, but on both sides, there were calls to adjust the 2008 guidance that created the current system.[1]

CONTINUED ON SP604

PAYER PERSPECTIVE

For Payers, Cost Is the Downside of Continuing Cardiovascular Outcomes Trials in Current Form

Kenneth Snow, MD, MBA

IT IS OF PARAMOUNT IMPORTANCE to a health plan that any therapy result in an improved clinical outcome. In addition, therapy should be priced in a way to keep healthcare and insurance costs as low as possible. Rising medication costs contribute to higher premium costs, making coverage less affordable.[1,2]

Payers are keenly interested in outcomes data. From their perspective, the goal of treatment for any disease state is not the treatment itself but rather an improvement in the outcome experienced by the member. In this way, the goal of the payer is aligned with the goal of the member. In the case of type 2 diabetes, before 2008

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FROM THE CHAIRMAN

Moving Beyond the Holy Grail

A DECADE AGO, concern that a blockbuster diabetes drug, rosiglitazone (Avandia), was causing heart attacks and possibly early cardiovascular death prompted the FDA to take an extraordinary step: requiring the makers of new type 2 diabetes therapies to conduct dedicated safety trials to show the drugs were safe. The trials would be large and expensive, and the rules would be strict. To no surprise, many were unhappy. But as Cleveland Clinic cardiologist Steven Nissen, MD, predicted, the trials would teach the diabetes and cardiology communities things they would otherwise have not known.

In October, an FDA advisory committee took a fresh look at these studies, known as cardiovascular outcomes trials, and asked, in short, whether they should continue. The answer, as explained in an interview with Mikhail N. Kosiborod, MD, FACC, FAHA, of Saint Luke's, is more complicated than yes or no, but it was clear that even those who voted against the question put to the panel saw value in the science that has occurred. The first glimmer of what was to come happened in June 2015 in Boston, Massachusetts, when Yale's Silvio Inzucchi, MD, was invited to comment on the results of the ELIXA trial for the glucagon-like peptide-1 receptor agonist lixisenatide (Lyxumia).

The results were neutral: The drug controlled glycated hemoglobin and did no cardiovascular harm, but it offered no benefit either. And then Inzucchi offered teasers that perked up ears in the room. Are investigators asking the right questions? Are they recruiting the right patients? "We as clinicians want to know a little more than safety," he said.

Given the risk profile of the patients, Inzucchi said that day, it might be "naïve" for doctors treating diabetes to believe they could affect cardiovascular outcomes too. But if a therapy could be shown to do this, "only then would we have achieved the holy grail," he said.[1]

Inzucchi, of course, was the lead investigator on EMPA-REG OUTCOME, and within months the trial's results would stun the diabetes community by showing that the sodium glucose cotransporter 2 inhibitor empagliflozin (Jardiance) had reduced cardiovascular death by 38% and all-cause mortality by 32%.[2]

As this issue discusses, diabetes care was forever changed. The idea that drugmakers would just have to show their products could control blood glucose was over; physicians and payers would now ask how therapies would prevent downstream results like heart attacks, strokes, and cardiovascular death. And as we move forward, new trial results will give us answers about preventing heart failure, kidney failure, and peripheral artery disease.

Kosiborod tempers the enthusiasm by noting that physicians must wait for new trial results before looking ahead to treating patients earlier in the disease cycle. But he, too, suggests that for patients with prediabetes, lifestyle changes are not the entire answer.

Diabetes affects 30 million Americans; prediabetes, 84 million. The cost of the disease in 2017 was $327 billion.[3] Arresting its progression and its consequences seems to be the best course for bending the cost curve in Medicare and beyond. Although it may be time for the FDA to adapt cardiovascular trials for the next wave of drug development, a decision made with safety in mind has yielded a bounty of benefits for patients. ◆

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Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

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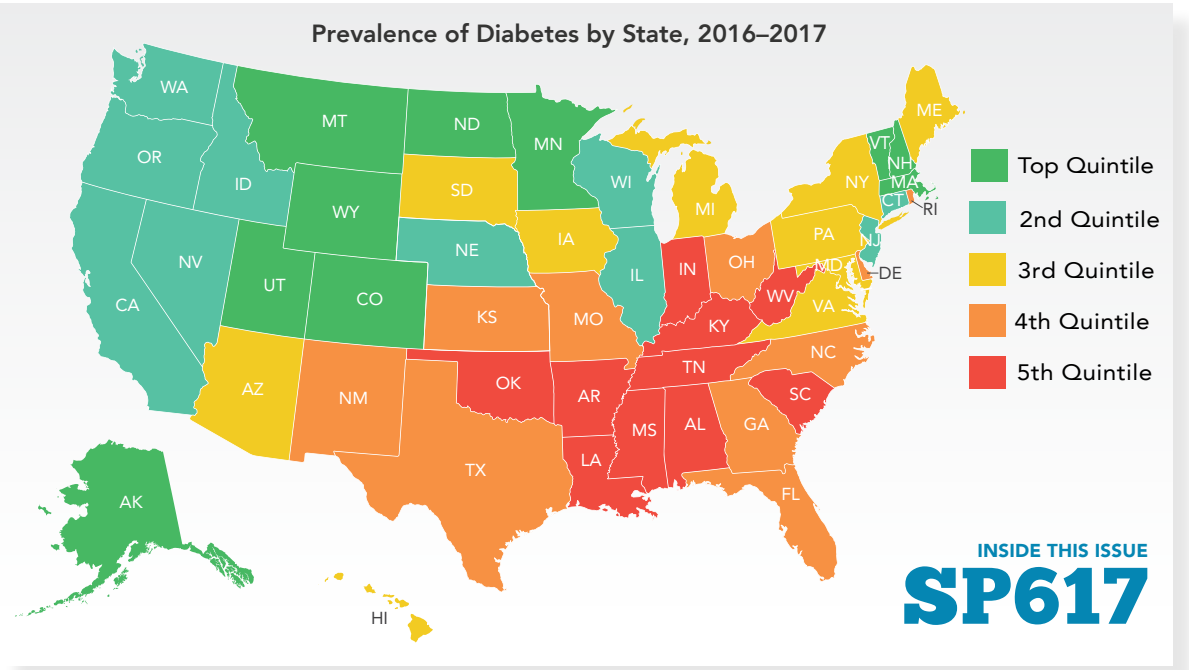

Findings from Gallup and Sharecare show how diabetes has spread across the United States.

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To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in diabetes.

INTERVIEW

Time for a "New Goalpost" in Cardiovascular Outcomes Trials, Kosiborod Suggests

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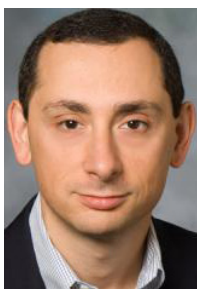

KOSIBOROD

Mikhail N. Kosiborod, MD, FACC, FAHA, clinical researcher, Saint Luke's MidAmerica Heart Institute; professor of medicine, University of Missouri-Kansas City School of Medicine.

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After an FDA advisory panel voted 10-9 on October 25, 2018,[4] to retain the trials, *EBDM* asked Kosiborod about the fresh look that regulators are taking at these practice-changing studies. While he acknowledged the criticisms about the restrictions and high costs of CVOTs, Kosiborod said that the FDA requirement has done much to advance the care for people with type 2 diabetes (T2D).

"The guidance, and the clinical trials and the data we learned from the trials—and we learned a tremendous amount over the past decade—were the catalysts for this complete, fundamental paradigm shift in how we approach type 2 diabetes management," he said. The narrow focus on lowering glycated hemoglobin (A1C) has been replaced with an emphasis on comprehensive risk reduction—looking not just at the laboratory values for type 2 diabetes control, but at what matters most to patients and clinicians—prevention of its deadly complications, "of which cardiovascular disease is number 1 in terms of impact."

Kosiborod, a cardiologist and clinical researcher at Saint Luke's Mid America Heart Institute and a professor of medicine at the University of Missouri –Kansas City School of Medicine, said both the ADA *Standards of Care*[5] and a recent statement from the ADA and EASD[6] now recommend "a completely separate approach for treatment of patients who have T2D and established cardiovascular disease."

"The overarching message is that the guidance has produced a lot of good. It has come at a [financial] cost, but it has dramatically changed how we think about diabetes management."

— Mikhail N. Kosiborod, MD, FACC, FAHA

"The only reason this has occurred is because of the large cardiovascular outcomes trials—the majority of which were done as a direct result of this guidance," he said.

The 10-9 vote obscured the consensus among members of the FDA Endocrinologic and Metabolic Drugs Advisory Committee that the trials have had a "huge [and] positive impact," Kosiborod said. "I don't think any of the panel members wanted to completely abandon the FDA guidance," he said. Rather, the discussion pointed toward updating CVOTs to reflect knowledge gained over the past decade.

"The overarching message is that the guidance has produced a lot of good. It has come at a [financial] cost, but it has dramatically changed how we think about diabetes management. Patients are clearly going to benefit from all the things we have learned," he said.

Like other experts, Kosiborod foresees a regulatory paradigm with different end points, more flexibility, and greater use of real-world evidence. CVOTs were designed primarily to prove that T2D drugs did not harm patients, not to show which drugs were superior to others. With multiple T2D therapies now demonstrating a cardiovascular benefit,[7-10] Kosiborod said that perhaps this is the new baseline. "That doesn't mean you don't do safety trials if you're just trying to prove that [a drug] is safe," he explained. "But for many of the compounds in development, the new goalpost should be that they are superior to whatever the comparator is, rather than noninferior."

What Would Updated CVOTs Look Like?

Kosiborod had several suggestions on where the large outcomes trials could go from here:

- **Less rigidity in the way CVOTs are constructed**. The 8 trials the FDA reviewed did not show increases in major adverse cardiovascular events (MACEs),[11] so future trials may need to prove that novel compounds are better than the alternatives. "If you have a compound you believe will provide a benefit, doing a cardiovascular superiority trial, rather than one for safety, may be a better construct," he said.
- **Redefining the primary end point**. FDA's guidance focuses on MACEs (see **Cover**) but Kosiborod notes that many other cardiovascular outcomes also matter in diabetes. "Heart failure is emerging as one of the most common cardiovascular complications, if not the most common in people with diabetes and the one associated with the worst prognosis of all known fatal cardiovascular events," he said. Having heart failure as primary end point is entirely appropriate, and Kosiborod praised investigators of the DECLARE trial for adding a coprimary end point of cardiovascular death or hospitalization for heart failure (HF). Shortly after the interview, DECLARE showed a reduction in this second end point, driven by the HF benefits.[12]
- **Mechanics of trial operations**. Kosiborod said the term "pragmatic trial" is discussed as a successor to the current format; this generally refers to simplifying the trial mechanics and even integrating the trial into clinical practice, but the field needs consensus on what that means. "I think that in some cases it's not easy to do pragmatic trials; there are always compromises that come with any relaxation of restrictions in which these clinical trials operate. But, if we are to really consider lowering the cost, we have to look at some ways in which they can be made more pragmatic," he said. Randomized registry trials, which don't require researchers to repeatedly construct "the machinery" of the trial, are 1 option, but there are limits here, too. "It's a very elegant concept," Kosiborod said. "The problem is that appropriate registries that provide high-quality data are limited to certain countries; not all that many countries can do it." Using patients from just a few countries is a problem if the results are to be generalizable.

- **Adjudicating end points.** FDA requires independent adjudication of end points, but Kosiborod said studies show investigator adjudication may produce the similar results without the added costs. "You need to look at it on a case-by-case basis," he said.

What Is the Role of Real-World Evidence?

Kosiborod is the lead investigator for CVD-REAL, which has used claims and registry data from multiple countries to show that SGLT2 inhibitors are associated with significantly lower risks of hospitalization for HF and death in patients with T2D, compared with patients who took other glucose-lowering therapies. Recent results published in June, based on data from South Korea, Japan, Singapore, Israel, Australia, and Canada, for example, found a 49% reduction in all-cause mortality and a 36% reduction in hospitalization for HF.[13]

"You have to evaluate real-word evidence just like you would evaluate any other piece of evidence," Kosiborod said, noting that as with a clinical trial, not all real-world evidence studies are of the same quality. Both real-world evidence studies and clinical trials have their own limitations. "Sometimes patients with the highest risk and the lowest risk are underrepresented in clinical trials," he said. With event-driven trials, "very low-risk patients are typically not included," because it would take too long for the trial to conclude.

In addition, he said, real world data may matter when evaluating health resource utilization and costs, and regulators are starting to pay more attention to it. "It will be interesting to see how the regulators incorporate real-world data into their decision making. I suspect that it's going to have a bigger role over time. But it will need to be used as a complement to clincial trial data, not a replacement for it."

New Therapies and Heart Failure

Kosiborod and other investigators recently published a research letter that examined an unanswered question from the EMPA-REG OUTCOME trial, the first to show a cardiovascular benefit in a T2D therapy, empagliflozin (Jardiance; Eli Lilly/Boehringer Ingelheim).[14] The letter asked whether the benefits seen in reducing cardiovascular death and hospitalization for HF were tied to a patient's baseline A1C or to A1C reduction during the trial. Kosiborod explained that several hundred patients in EMPA REG OUTCOME screened at 7% A1C to meet the trial criteria but were below that level at the time of randomization. Kosiborod and his colleagues were able to show that the cardiovascular benefits seen in this trial were independent of a patient's baseline A1C or a to A1C reduction during the course of the trial.[15]

This adds to the growing body of data that the benefits of SGLT2 inhibitors, including prevention of heart failure, are likely to be independent of their glucose-lowering effects.

Does these results add to the sense that SGLT2 inhibitors have a future role in prevention of heart failure? And if so, could patients benefit even if they don't have diabetes?

Not so fast, said Kosiborod.

"We can speculate that maybe that's the case, but of course, we don't know," he said, warning that discussing broader use of SGLT2 inhibitors is premature because all the published studies to date involve patients with diabetes. "We will have to wait for those answers, but they will be coming."

He mentioned several trials that will examine these questions:

- The **EMPEROR trials** (EMPEROR Preserved, for HF patients with preserved ejection fraction, and EMPEROR Reduced, for HF patients with reduced ejection fraction) are studying the safety and efficacy of 10 mg per day of empagliflozin in patients with heart failure both with and without diabetes.[16]
- The **DAPA-HF** and **DELIVER trials** are evaluating the effects of dapagliflozin (Farxiga, AstraZeneca) in patients with heart failure with reduced and preserved ejection fraction, respectively, in patients both with and without T2D.[17,18]
- The **SOLOIST trial** will examine the effect of sotagliflozin, a dual SGLT1/2 inhibitor, (Zynquista; Sanofi) in patients with T2D and worsening HF.[19]

Looking Toward Earlier Intervention

Medicare is now funding the Diabetes Prevention Program,[20] which has shown that lifestyle interventions can be effective in the near term: The landmark study found a 58% reduction in progression to T2D, compared with metformin. Although 15-year results have shown that over the long haul, the percentage of patients who progress to T2D is about the same, the patients in the lifestyle intervention at least took much longer to get there.[21]

The simple fact is, it's hard to stick with a healthy diet and exercise. Should clinicians be doing more early on? "We know that people with prediabetes are also at elevated risk of cardiovascular complications—probably not as much as people with manifest diabetes, but certainly higher than people with normoglycemia. It's so important to understand what we can do to lower that risk," Kosiborod said.

"Lifestyle changes are the foundational therapy for people with diabetes, and I believe for people with prediabetes, and this is where we should start. However, I don't think it's where we should end."

Lifestyle modification is probably not enough for most people with prediabetes, because sticking with regimens long-term is so difficult. There's a lot to learn in the coming years, Kosiborod said, about whether SGLT2 inhibitors and GLP-1 receptor agonists have a role for those who have not progressed to T2D. The DISCOVER study across 38 countries just reported how widespread the microvascular and macrovascular complications are for people with T2D, and how early these problems develop.[22] Similarly, Kosiborod said he is interested in results from a trial that treated patients with obesity and cardiovascular complications with GLP-1 receptor agonists.[23] Such a trial may help convince payers to treat obesity more aggressively, as some have been reluctant to pay for therapies.

"When it comes to cost, we really need to keep a holistic view," Kosiborod said. While medications have a cost, events like heart failure, heart attacks, and strokes, progression of kidney disease, etc.—which bring high costs to the healthcare system and can leave patients disabled—have a cost to society as well, he said. Both HF and chronic kidney disease, 2 long-term cardiovascular complications, are not only expensive but reduce quality of life for patients.

Kosiborod is excited about the results that will be reported over the next 5 years. "It's an incredibly exciting time in the field," he said, comparing today's choices for people with T2D with those available in 2008, when there were fears that medications were causing patients harm. "It's a real milestone, something that is extremely exciting to see. The field is evolving to where we have multiple evidence-based treatments with really tangible benefits to patients." ◆

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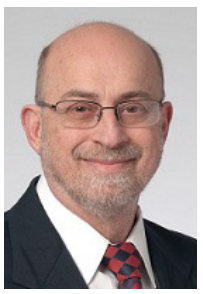
REGULATORY UPDATE

After FDA Panel Vote, Some See "Next Generation" of Cardiovascular Safety Trials for Diabetes Drugs

Mary Caffrey



NISSEN

Steven Nissen, MD, Cleveland Clinic, authored a 2007 meta-analysis that led to the FDA guidance requiring cardiovascular outcomes trials.

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"We now have 8 clinical trials conducted under the guidance. All 8 have demonstrated no excess cardiovascular risk with any of the therapies studied," wrote William Chong, MD, acting director of the FDA's Division of Metabolism and Endocrinology Products, in an analysis presented to panel members ahead of the meeting. "Notably, [results of] some of the trials have shown a reduced risk for adverse cardiovascular events."[2]

It is not so simple, said Steven Nissen, MD, of the Cleveland Clinic, in an interview with *Evidence-Based Diabetes Management*™ (*EBDM*) ahead of the meeting. Nissen's 2007 meta-analysis of rosiglitazone in the *New England Journal of Medicine*,[3] which suggested an increased risk of myocardial infarction and cardiovascular death, led to the 2-step process that he recommended, which guides drug development for T2D to this day. At the time, he received backing from cardiologist Robert Califf, MD, who would go on to become FDA commissioner.[4]

Conducting CVOTs would lead to more than their expressed purpose of informing physicians and the FDA about whether drugs for T2D increased the risk of major adverse cardiovascular events (MACEs), Nissen predicted. "We also knew that if you did outcomes trials, you would learn things you didn't otherwise know," he said.

For example, he said, CVOTs have caused the FDA to add information about heart failure risk to the label of saxagliptin (Onglyza/Bristol-Myers Squibb),[5] and the trial for canagliflozin (Invokana), the sodium-glucose cotransporter 2 (SGLT2) inhibitor, showed an increased risk for lower-limb amputations.[6]

At the same time, results of other trials have shown that SGLT2 inhibitors appear to have cardiovascular benefits,[6,7] as does the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide (Victoza).[8] Novo Nordisk, which makes liraglutide, announced in late November that top-line results of the PIONEER 6 trial showed that another GLP-1 receptor agonist, oral semaglutide, reduces cardiovascular and all-cause mortality risk but not the overall number of cardiovascular events.[9] Nissen noted that results of CVOTs have shown that GLP-1 receptor agonists do not cause pancreatitis, which had been a concern.

The FDA's guidance sets standards that allow drugs for T2D to reach the market, while these giant randomized controlled trials often continue in a postmarketing phase, depending on the phase 2 and 3 results (see **Table**). The trials are huge, involving thousands of patients and laboratories around the world to ensure the studies are adequately powered. As a result, some stakeholders argue that the trials have become too expensive and stifle innovation while driving up the cost of drugs currently on the market.

Nissen said using claims data and other "real-world" observational sources just would not do, and 2 of the 3 experts who testified before the FDA—cardiologist Marc Sabatine, MD, MPH, of Harvard Medical School and the TIMI Study Group, and Jennifer Green, MD, of the Duke Clinical Research Institute—agreed. "Adequately powered and randomized CVOTs of individual agents should continue," Green said. "There is no substitute."

"I don't think loosening regulatory standards is good public policy," Nissen said in the interview with *EBDM*. He added that it was "unlikely" that doing so would make drugs for T2D less expensive.

But Robert Ratner, MD, former chief scientific and medical officer at the American Diabetes Association (ADA) and now with Georgetown University, and several panelists said the knowledge gained from the first decade of CVOTs could allow the FDA to recommend adjustments, which would make premarket trials

stronger and more streamlined. Nissen agrees there are approaches that can achieve this goal without going back to pre-2008 standards. Among the ideas offered during the meeting:

- Strengthen the phase 2 and 3 trial requirements and require CVOTs only if a signal is detected.
- Tighten premarket requirements, and use registry or observational data to detect safety signals post approval.
- Add premarket requirements beyond MACE for other safety issues, based on findings in the first decade of CVOTs.

CVOTs have prompted major professional societies, including the ADA and the American College of Cardiology (ACC), to update their clinical guidelines based on findings about newer classes of therapy, especially SGLT2 inhibitors GLP-1 receptor agonists (see **SP610-SP613**). And pharmaceutical companies have gone back to the FDA to add cardiovascular indications after their initial drug approvals to gain a leg up in the market.[10-12]

The ADA published a paper in January 2018 that discussed the issues surrounding CVOTs; the authors rejected the idea that the trials were discouraging drug development but acknowledged their contribution to drug costs.[13] ACC Vice President Richard Kovacs, MD, FACC, similarly cited the FDA panel's effort to balance competing concerns in an email to *EBDM*:

"Over the course of the last decade, our awareness of the connection between diabetes treatments and cardiovascular outcomes has increased tremendously. Outcomes trials performed since publication of the guidance provided us with a great deal of additional information, but they also raised many new questions. The Committee has appropriately highlighted the need for pausing to consider whether we have the correct information or whether we should be asking different questions and/or using different types of trials. The information generated by the guidance has forced clinicians to face the realities of cost and value consideration, generating winners and losers among the drugs under development."

In the January paper in *Diabetes Care*,[13] authors led by William T. Cefalu, MD, the ADA's current chief scientific, medical, and mission officer, offered several ways in which "the next generation of diabetes trials should be smarter, simpler, and innovatively designed to make more efficient use of resources and produce more generalizable results while still addressing safety issues." Suggested areas for improvement included:

- **Involvement of lower-risk populations.** Because the FDA sought to show that new therapies for diabetes were safe, the guidance called for studying patients with higher levels of cardiovascular risk. But some trial designs have included only those with advanced cardiovascular disease and failed to measure whether a therapy could stop it from advancing. Larger, longer trials would tell investigators more about the value of therapies in prevention.
- **Longer-term follow-up.** The ADA authors suggested innovative trial designs that include lifelong follow-up through electronic health records (EHRs), along with FDA approval of methods to track clinical outcomes in this manner. Such trials would give more information about cost-effectiveness, they wrote.
- **Comparisons of drugs.** The authors noted the need for trials with other therapies as a control, including tests of combinations of drugs known to be cardioprotective. Cost sharing between pharmaceutical companies should be encouraged to free up resources for innovation.
- **Diverse trial designs.** Methods that use big data, or factorial designs that test multiple interventions at once, are more efficient. Pragmatic trials that make use of health systems' EHRs can boost treatment persistence. Data from earlier trials can help investigators modify how the analysis is conducted, especially if they are exploring new end points.
- **Inclusion of advocacy groups.** Patient-reported outcomes should be included in future studies, and digital reporting tools can increase these abilities.

Although some have cited the cost of CVOTs to pharmaceutical companies, the trials have also helped drugs like empagliflozin (Jardiance; Boehringer Ingelheim/Eli Lilly) stand apart from competitors; the SGLT2 inhibitor was the first to demonstrate a cardiovascular benefit in the EMPA-REG OUTCOME trial, according to results released in September 2015.[7]

Thomas Seck, MD, vice president of US clinical development and medical affairs, primary care, at Boehringer Ingelheim, said in an interview with *EBDM* that the FDA guidance changed the discussion about glucose-lowering agents. "To say [an] agent should not increase the risk of cardiovascular events was not only appropriate, [but] it was something that society in general should expect," he said.

Seck shares the view that broader use of real-world evidence would be useful, and he would like to see more flexibility to allow more attention to other end points, including heart failure. "This would add more information for patients and for the healthcare system overall," he noted. ◆

TABLE. Requirements for Cardiovascular Outcomes Trials for Type 2 Diabetes Therapy

Phase 2 and 3 trials should: • Include patients at high risk for CV events • Be of sufficient size and duration to capture enough CV events to allow adequate evaluation of a therapy's CV risk • Include required major adverse cardiovascular events: CV mortality, myocardial infarction, and nonfatal stroke • Include events such as hospitalization for heart failure, revascularization procedures, and hospitalization for acute coronary syndrome
All CV events must be independently adjudicated.
A meta-analysis of the phase 2/3 program will follow a predetermined protocol, which specifies end points and statistical methods.
Premarketing data will compare CV events in a group taking study therapy with those in a control group, demonstrating that the upper limit of a 2-sided 95% CI of the estimated risk ratio is <1.8. If this cannot be done, it will be undertaken through a separate, large CV safety trial.
When 95% CI upper limit falls between 1.3 and 1.8 in the premarketing phase, the postmarketing phase will need to show that the upper limit of the 2-sided CI is <1.3 with a "reassuring" point estimate of overall CV risk.
These data should come from a dedicated cardiovascular outcomes trial that may begin during phase 2 and continue through the postmarketing period but cannot come through a meta-analysis of multiple phase 2 and 3 trials.

CV indicates cardiovascular.

Sources: 2008 FDA Guidance on Cardiovascular Outcomes Trials, American Diabetes Association

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PAYER PERSPECTIVE

For Payers, Cost Is the Downside of Continuing Cardiovascular Outcomes Trials in Current Form

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SNOW

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the prevailing thinking was that an agent that improved glycemic control would result in better outcomes, including cardiovascular outcomes. The recognition that improved glycated hemoglobin did not necessarily lead to a guaranteed improvement in cardiovascular outcomes resulted in the FDA's decision to require randomized, adjudicated trials to establish hazard ratios for major adverse cardiovascular events.[3]

The recent assessment by the FDA questioned the need for continuing the process of requiring cardiovascular outcomes trials for diabetes medications. The FDA Endocrinologic and Metabolic Drugs Advisory Committee voted 10-9 to continue the current process. This vote affirmed the view that the current requirements assessing the need for cardiovascular safety should remain in place. In the past decade, results from 8 studies have shown no increased risk of adverse cardiovascular events.[4] Yet the importance of knowing that the current approach to assess therapy to make sure that these medications would not lead to worse outcomes led to the decision. This logic is aligned with a payer's concern for improved outcomes. For diabetes and glycemic control, this means making certain that an improvement in glycemic control does not come at the unacceptable cost of worsened cardiovascular outcomes.

This decision, however, comes with a downside. The current system requiring cardiovascular outcomes trials increases the cost of drug development. Pharmaceutical companies take the cost of these trials into consideration as they price their drugs. This fact was a consistent theme cited by those who voted to see the current process changed. Questions were raised about alternative ways to provide adequate evidence to assess safety of potential drugs but in a more cost-effective manner. A number of different assessment processes were proposed, but in the end, none proved adequate to convince a majority of the committee.

The impact of this decision is significant. The cost of drug therapy is of major concern and contributes significantly to the ever-increasing cost of healthcare and health insurance. As the cost of bringing a drug to market increases, pharmaceutical companies pass that increase along to the payer. Regardless of whether the payer is a health insurance company or a pharmacy benefit manager, the acquisition price becomes higher. This cost must then be passed along to those buying coverage, leading to higher premiums and greater cost for the patient. Both factors can have significant consequences for care. Higher premiums can result in fewer people being able to afford health insurance.[5,6] Higher drug costs for a patient, particularly in the case of diabetes, have been shown to increase the likelihood of nonadherence or nonpersistence.[7] Thus, this cost decision does ultimately negatively affect the clinical outcome that was the primary driver of the decision in the first place.

Moving forward, 2 developments will prove crucial to whether the requirement for cardiovascular outcomes trials continues. The first centers on the results of ongoing trials or those required in the future. If the current trend continues and these trials do not uncover new cardiovascular risk findings but rather serve as a very expensive confirmation of the cardiovascular safety evidenced in previous studies, the necessity of these trials becomes less clear. Secondly, the use of big data is becoming more commonplace and accepted in many aspects of medical care. Future safety studies may well depend on the use of large databases with propensity-matched controls rather than controlled trials. Trials using big data can involve far greater numbers of subjects than do current trials and may prove to be a comparable or potentially superior approach to answering these safety questions. This type of research can also be done at a fraction of the cost of traditional trials.

The cost of drug development in many ways must follow the current trends in all aspects of the delivery of healthcare. New approaches to the provision of care—whether through technology, location, manpower, or research—are rapidly driving change in the healthcare system, with the goal to maintain or improve the quality of care while keeping it affordable. ◆

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Clinical Evidence for and Cost-Effectiveness of Advanced Cellular Tissue Products for the Treatment of Diabetic Foot Ulcers

Robert S. Kirsner, MD, PhD

AN ESTIMATED 30 MILLION Americans are living with diabetes. Additionally, 84 million have prediabetes, a condition that will result in type 2 diabetes within 5 years if not properly treated.[1] Long regarded as one of the most prevalent chronic diseases in United States, diabetes is also a leading cause of disability and the seventh-leading cause of death.[2] Less discussed is one of the most common complications of diabetes: diabetic foot ulcers (DFUs). If not properly treated with standard and adjunctive care, these chronic wounds can lead to permanent disability and premature death.[3] Although DFUs are not an inevitable comorbidity of diabetes, it has been estimated that the annual risk of developing a DFU may be as high as 4% and the lifetime risk may be as high as 34%.[4]

Without prompt intervention and proper treatment, DFUs will not heal, can cause soft tissue and/or bone infection, and may eventually require amputation of the affected limb or appendage. Unfortunately, this is not uncommon, as 1 in 6 patients with a DFU will undergo an amputation—making DFUs the leading cause of nontraumatic amputations in the country.[5] Given the prevalence and risks associated with DFUs, it is imperative that clinicians understand, have access to, and use the best available science for the treatment of these hard-to-heal wounds.

Results from research have shown that despite substantially higher up-front cost, advanced care that includes cellular tissue products leads to long-term cost savings in the context of total cost of care related to diabetic foot ulcers. A meta-analysis of several dozen economic evaluations of cell-based tissue products found that their use resulted in shorter wound treatment periods, which, in turn, led to fewer complications and in-treatment episodes.

In its recently released research compendium *Diagnosis and Management of Diabetic Foot Complications*, the American Diabetes Association (ADA) provides a comprehensive overview of the latest approaches for the management and treatment of DFUs and their complications. Produced by leading international DFU authorities, the compendium includes information about the use of adjunctive therapies, such as hyperbaric oxygen and negative pressure wound therapy, in instances in which DFUs do not respond to standard treatment.[5] Among the treatments highlighted in the compendium that garnered the most attention were advanced cellular tissue products (CTPs). These are bioengineered cell-based therapies that supply the wound with the cells, tissues, proteins, and growth factors needed to support the healing process.

In addition to being supported by a wide body of clinical evidence demonstrating their effectiveness in facilitating wound healing, advanced CTPs have also been shown to generate significant cost savings for payers and the US healthcare system overall. This article will review the clinical evidence highlighted in the compendium demonstrating the effectiveness of CTPs in wound healing. It will also review recent literature supplemented by my own experience suggesting there are long-term cost benefits associated with using these therapies.

Advanced CTPs: Clinically Effective DFU Treatment

Patients with DFUs who are not responding to standard care are at great risk of not having their wounds heal and can suffer dire consequences. In practice, we clinicians see this reality daily as patients whose DFUs are not properly treated face increased risk of limb amputation, which results in higher mortality rates. Despite the availability of new therapies, DFUs remain notoriously difficult to treat. As most patients first experience a loss of feeling in the foot due to neuropathy, it is common for patients and providers to fail to notice a DFU until weeks after it has developed. Therefore, it is often recommended that clinicians be aware that advanced care may be required to ensure complete healing.[6] In my practice, the use of advanced therapies has undoubtedly saved many limbs and lives.

Though treatment approaches for DFUs vary according to wound severity, clinicians commonly use an intensive adjunctive therapy in instances in which standard treatment—which typically consists of debridement, infection control, off-loading, and appropriate dressing—is not sufficient to reduce wound size over the first few weeks of care and/or close the wound in a timely fashion. In recent years, several innovative, advanced therapies have been developed for the treatment of DFUs, presenting new opportunities to better treat patients and minimize common risky and costly complications.

The compendium highlights 2 types of advanced, bioengineered CTPs used in adjunctive treatment of DFUs: an allogeneic bilayered human skin equivalent (HSE) and a dermal skin substitute (DSS). Unlike other types of CTPs, these are unique because they are cellular constructs and are both FDA-approved class III medical devices indicated specifically for the treatment of DFUs. To date, these are the only such therapies in their product class approved for this purpose.

Like human skin, HSE consists of 2 layers, has living cells, and contains structural proteins. The underside, or dermal, layer comprises a protein matrix of bovine type 1 collagen and neonatal human fibroblasts, while the epidermal layer consists of a stratified epithelium containing neonatal keratinocytes. Other components normally found in human skin—such as melanocytes, Langerhans cells, macrophages, and lymphocytes, as well as structures such as blood vessels, hair follicles, and sweat glands—are absent.

Two randomized controlled trials cited in the compendium have confirmed that patients treated with HSE showed significantly higher rates of healing and a shorter time to full wound closure than patients receiving standard care, making HSE among the best studied of all CTP therapies.[7,8] The results of these rigorous trials led to HSE's premarket approval by the FDA. Results from other studies not included in the compendium show HSE to be effective compared with other types of therapies. For example, a comparison study in a real-world setting found that treatment with an HSE increased the probability of healing by 97% compared with treatment with a dehydrated human amnion/chorion membrane, suggesting added benefit or that it was used more appropriately in practice.[9]

The dermal cellular CTP, DSS, is a single-layered construct of neonatal fibroblasts grown on absorbable mesh scaffold. The DSS delivers metabolically active human fibroblasts to a wound via a bioabsorable polyglactin mesh scaffold. Applying DSS imparts the benefits of human collagen, extracellular matrix proteins, and cytokines and other growth factors necessary for healing.

Among the studies cited by the ADA compendium, one large trial found that among patients with DFUs that have been present for more than 6 weeks, weekly application of the DSS resulted in significantly higher healing rates. Furthermore, treated patients were nearly twice as likely to have complete wound closure than those not treated with the DSS.[10] Results of additional »

studies of patients treated with the DSS corroborate these findings. A study of patients with DFUs treated with the DSS found that 30% had achieved complete wound closure by week 12 compared with only 18.3% in the control group.[11] Wounds treated with DSS—compared with other CTPs—were more likely to experience complete wound closure by week 12 (55% vs 32%) and week 24 (76% vs 50%) and had a significantly shorter mean time to full wound closure, evidence that DSS is perhaps among the most effective CTPs to date[12]

Advanced CTPs: A Cost-Effective Solution

The cost of DFU treatment to the US health system is shockingly high—as much as $15 billion by some estimates.[13,14] Another report found that treatment of DFUs may account for at least 33% of the direct medical costs associated with diabetes mellitus and that the cost to care for patients with DFUs is 5.4 times higher than the cost of care for those without them.[15] The vast majority of these costs are related to patients with DFUs incurring higher emergency medical costs and being more likely overall to be admitted to the hospital. DFUs and related complications are one of the major reasons for hospitalizations among patients with diabetes.[16-18]

Considering that foot ulcer reoccurrence is quite common and roughly 50% of all patients have a reoccurrence within 1 year after ulcer healing,[5] it is important for clinicians to be equipped with the means to most effectively treat DFUs to help minimize hospitalizations, infections, and other associated complications that contribute to long-term costs.

Results from research have shown that despite the substantially higher upfront cost, advanced care that includes CTPs leads to long-term cost savings in the context of total cost of care related to DFUs. A meta-analysis of several dozen economic evaluations of cell-based tissue products found that CTPs resulted in shorter wound treatment periods, which, in turn, led to fewer complications and inpatient episodes.[19] In other words, the more quickly a DFU progresses to closure, the lower the risk is of infection or other complications that can stall wound healing and result in costly surgeries and hospitalizations.

A more recent analysis that exclusively examined patients treated with cellular CTPs found that although patients received more intensive physician office and outpatient care, those costs were more than offset by reductions in lower-limb amputations and hospitalizations.[20] The investigators in that study examined administrative claims data from Medicare beneficiaries between 2006 and 2012 and found that patients treated with CTPs had significantly lower amputation rates, fewer days hospitalized, and fewer emergency department visits than the control group, who received only standard care. During the 18-month follow-up period after treatment, average per-patient costs for treatment with an HSE were $5253 lower than those of the matched control. Patients treated with a DSS had costs $6991 lower than those of the control. These findings appear to be consistent with previous research showing reductions in lower-limb amputations and other resource-intensive health-care procedures.[21-22]

In addition to improving healing, treatment of non–self-healing wounds with the products described above has the potential to lead to significant cost savings by reducing DFU-related complications such as osteomyelitis and amputation. An individual practitioner with a busy practice may reduce overall costs by tens or hundreds of thousands of dollars annually by using an advanced CTP in situations in which wound healing has not progressed using standard treatment.

Conclusion

Despite recent progress in the treatment of DFUs, these wounds remain a significant public health problem that will continue to require rigorous and evidence-based clinical practices. Proper use of evidence-based advanced adjunctive therapy is warranted. Advanced CTPs have shown promising scientific results for the treatment of DFUs, in terms of both their clinical efficacy and the cost savings associated with shorter healing times and reduced risk of infection and related acute episodes and surgeries.

As clinicians, health systems, payers, and patient advocates grapple with how best to address this public health crisis, they would do well to consider the full suite of therapeutic options available and to use advanced interventions, when appropriate, that are clinically proved to help save limbs and lives. ◆

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DISCLOSURES

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Increasing Awareness About Peripheral Artery Disease Can Save Limbs and Lives

Foluso A. Fakorede, MD

WITH THE HOLIDAY SEASON in full force, most Americans are looking forward to feasting with family and friends and taking a much-needed break from work.

However, for the more than 30 million US individuals living with diabetes and the 84.1 million living with prediabetes,[1] the consumption of unhealthy food and long periods of inactivity during the season can make symptoms worse. Diabetes is a public health crisis, costing $327 billion per year, according to the most recent analysis from the American Diabetes Association.[2] As many as 1 in 3 US adults could have diabetes by 2050 if current trends continue, according to an analysis based on CDC data.[3] Racial and ethnic minorities have a higher prevalence of the disease and a greater burden compared with white individuals, as disparities in health and healthcare lead to higher rates of complications in minority populations. Unfortunately, these communities may lack awareness of complications and the symptoms that can signal a need for medical attention.

FAKOREDE

One important complication of diabetes is atherosclerosis. Atherosclerosis refers to the hardening of the arteries and the accumulation of fatty deposits within them. Arteries are delicate tubes that carry blood with oxygen and nutrients to all parts of the body. As such, there is no room for plaque, which narrows these vessels and restricts the blood flowing through them. Severe narrowing can block blood flow to areas such as the brain, the heart, and the legs, leading to devastating results, especially if affected individuals do not recognize the symptoms in time to get help. A lack of blood flow can cause the death of heart muscle; if the brain is affected, a stroke can occur; and reduced flow in the legs can lead to pain, poor healing of diabetic ulcers, gangrene, and eventual amputation.

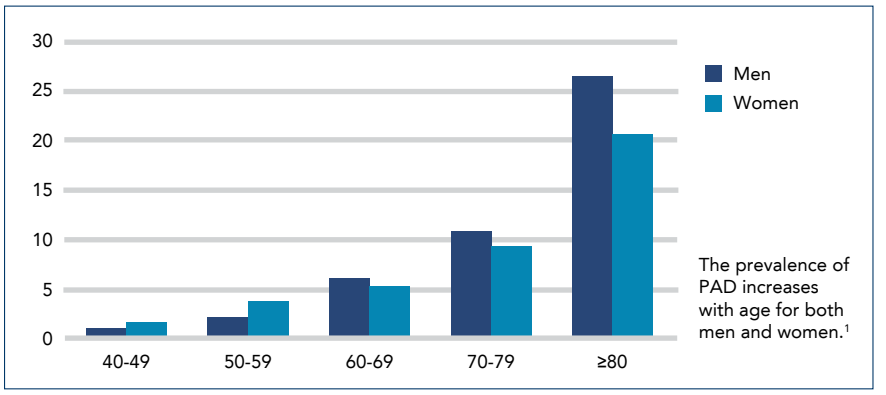
Atherosclerosis that affects the limbs is called peripheral artery disease (PAD), the complication that has been shown to cause the most significant long-term disability and economic burden in patients with diabetes. It is estimated that 1 in 3 people 50 years or older with diabetes has PAD, yet millions of people with the disease do not realize they are at risk for losing a limb until it is too late.[4] Someone is given a diabetes diagnosis every 17 seconds in the United States, and every day, 230 Americans with diabetes will undergo an amputation.[5] Each year, approximately 200,000 nontraumatic amputations occur in the United States. African Americans are 4 times more likely to experience diabetes-related amputation than white individuals, and it is estimated that throughout the world, a leg is amputated every 30 seconds; 85% of those amputations are the result of a diabetic foot ulcer.[6]

Unfortunately, even as the diabetes and PAD epidemics worsen, people do not recognize the symptoms. Early detection and treatment of PAD is crucial to saving limbs. With timely screening, in-depth assessment of symptoms, and thorough physical examinations, millions of amputations can be prevented. Like cancer, PAD must be caught early and treated to prevent progression and suffering. It is often asymptomatic in its early stages, making ultrasound screenings a lifesaving necessity.

As a limb salvage specialist, I am committed to educating and providing quality healthcare to prevent the loss of limbs. Early screening, diagnosis, and intervention save legs and thus preserve quality of life. More important, they save lives, as 50% of patients with diabetes who experience amputation will die within 2 years of the amputation.[7]

To help prevent complications from diabetes and PAD, it is important for everyone to manage this disease every day. A little physical activity goes a long way in soothing leg pain and keeping blood flowing to the legs and feet. Controlling blood sugar, knowing your glycated hemoglobin number, and eating a well-balanced diet designed for those with diabetes can significantly reduce the risks for PAD and amputations. By quitting smoking, individuals can also greatly reduce their risk for PAD.[8]

FIGURE. Prevalence of PAD (%) by Age Group (Years)



PAD indicates peripheral artery disease.
Source: CDC

On a national scale, I recently joined a group of advocates in Washington, DC, to call on lawmakers to adopt a national strategy to increase public awareness of PAD. This distinguished group of advocates included both physicians and patients who have endured amputations and who had a shared mission to change policy to help prevent unnecessary limb loss. PAD advocates are asking the Trump administration to convene an intragovernmental workgroup to develop a standardized model for amputation reduction and to raise awareness of this critical issue.

Regardless of whether people with diabetes feel leg pain, they should be encouraged to talk with their doctor and be screened for PAD. Physicians should take patients' shoes off at every appointment and teach patients to examine their own feet. Helping patients take control of their health could literally save limbs—and lives. ◆

AUTHOR INFORMATION

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GUIDELINES UPDATE

ADA/EASD Release Joint Statement on Managing Hyperglycemia in Type 2 Diabetes

Mary Caffrey

ONGOING ACCESS TO DIABETES self-management education and support (DSMES) and promoting good medication adherence are among the keys to managing hyperglycemia, or high blood glucose, in patients with type 2 diabetes (T2D), according to a joint statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), released October 5, 2018, at the EASD annual meeting in Munich, Germany.

The consensus statement also called for patients with cardiovascular disease to be treated with 1 of the 2 novel classes that have been shown to have cardiovascular benefits: a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist.

The statement was published in *Diabetologia,*[1] the official journal of EASD, and in *Diabetes Care*, the official journal of ADA. The joint statement followed ADA's recommendations in late 2017 that certain SGLT2 inhibitors and a GLP-1 receptor agonist had cardiovascular benefits; these recommendations appeared in the organization's 2018 *Standards of Medical Care in Diabetes.*[2]

The experts who developed the ADA/EASD consensus statement said that patient preference should be a major factor in driving treatment choices, because their preferences for the delivery method—such as a pill versus an injection—or things like adverse effects or cost, could affect adherence. Further, the medications cannot work if patients do not take them, regardless of what evidence showed in a clinical trial.

The emphasis on giving patients more access to DSMES is key, because current reimbursement models, including those in Medicare, may limit the number of hours or points at which a patient can meet with a diabetes educator. Although there are new digital diabetes management tools available, evidence shows that these work best when patients can combine them with contact with a trained professional.[3] A position statement from the American Association of Diabetes Educators, ADA, and the Academy of Nutrition and Dietetics called for education at discrete points in the life cycle of diabetes: (1) at diagnosis, (2) at annual assessments, (3) when new complications occur, and (4) during transitions in life and care.[4]

Among other recommendations, the ADA/EASD consensus statement[5] calls for:

- Advising patients who are overweight or obese with diabetes to start a lifestyle management program, including food substitution where appropriate.
- Boosting physical activity to improve glycemic control.
- Making metabolic surgery available to adults with T2D who have a body mass index (BMI) of at least 40 (or ≥37.5 with Asian ancestry) or a BMI of 35 to 39.9 (32.5-37.4 with Asian ancestry) who have comorbidities and have not achieved weight loss goals with nonsurgical methods.
- Metformin as first-line therapy, but for patients with clinical cardiovascular disease, an SGLT2 inhibitor or GLP-1 receptor agonist with a demonstrated cardiovascular benefit is recommended.
- Considering an SGLT2 inhibitor with proven benefts for patients with chronic kidney disease or clinical heart failure and atherosclerotic cardiovascular disease.
- Making GLP-1 receptor agonists the first injectable considered, except if type 1 diabetes is a possibility.

Experts called for more research into combinations of glucose-lowering therapies. "As cost implications for these various approaches is enormous, evidence is desperately needed," the panel said in a statement. "Defining optimal cost-effective approaches to care, particularly in the management of patients—including those with multi-morbidity—is essential."[5]

The panel said the giant cardiovascular outcomes trials raise important questions: Do benefits, including renal benefits, extend to low-risk patients? If so, for which population groups?

Shortly after the joint statement, an FDA advisory panel agreed to continue the cardiovascular outcomes trials that have demonstrated unexpected cardiovascular benefits in T2D (see **Cover**). However, the panelists discussed the possibility of making adjustments to the trials to examine different outcomes and to bring down their cost. Since the emergence of unanticipated benefits in newer therapeutic classes for T2D—notably SGLT2 inhibitors—some pharmaceutical companies have launched trials to specifically examine heart failure or renal outcomes.[6-8]

"The management of hyperglycemia in type 2 diabetes has become extraordinarily complex with the number of glucose-lowering medications now available," the authors wrote. "Patient-centered decision making and support and consistent efforts to improve diet and exercise remain the foundation of all glycemic management. Initial use of metformin, followed by addition of glucose-lowering medications based on patient comorbidities and concerns is recommended as we await answers to the many questions that remain." ◆

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GUIDELINES UPDATE

ACC Pathway Finds Empagliflozin "Preferred" SGLT2 Therapy for Patients With Type 2 Diabetes, ASCVD

Mary Caffrey

A NEW AMERICAN COLLEGE OF CARDIOLOGY (ACC) Expert Consensus Decision Pathway states that empagliflozin is the preferred therapy among sodium-glucose cotransporter 2 (SGLT2) inhibitors for patients with type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (ASCVD).

The pathway document, which features a chart to guide cardiologists in clinical practice, was published November 26, 2018, in the *Journal of the American College of Cardiology* (*JACC*).[1] The consensus document also finds that liraglutide is the preferred treatment among a second novel class of T2D treatments, the glucagon-like peptide-1 (GLP-1) receptor agonists.

Empagliflozin is sold as Jardiance by Boehringer Ingelheim and Eli Lilly; liraglutide is sold as Victoza by Novo Nordisk.

Although cardiovascular disease remains the leading cause of morbidity and mortality in patients with T2D, the authors write that, until recently, medications to achieve glycemic control were not expected to offer any cardiovascular benefit. "The recent development of [2] novel classes of therapies—SGLT2 inhibitors and GLP-1 [receptor agonists]—has, for the first time, demonstrated that treatments developed for glucose lowering can directly improve outcomes," wrote Writing Committee co-chairs Sandeep R. Das, MD, MPH, FACC; Brendan M. Everett, MD, MPH, FACC; and their colleagues.

SGLT2 inhibitors work through a unique mechanism of action that targets a protein responsible for the reuptake of glucose; as a result, the body expels excess glucose through the urine. A person with type 2 diabetes can lose as much as 100 mg glucose a day. Researchers are still working to fully understand this mechanism.

Having ACC weigh in on how cardiologists should treat patients with T2D represents a paradigm shift in treating the disease, but one that is a natural evolution given developments since 2015 in research, treatment, and guidelines from major organizations engaged in diabetes care. On October 5, 2018, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes jointly updated their consensus statement on the management of hyperglycemia to include SGLT2 inhibitors and GLP-1 receptor agonists.[2]

ADA endorsed the ACC pathway, and William T. Cefalu, MD, ADA's chief scientific, medical, and mission officer, served as an author on the *JACC* article.

Thomas Seck, MD, vice president of US Clinical Development and Medical Affairs, Primary Care, at Boehringer Ingelheim, shared the authors' appreciation for the change in thinking about shared responsibilities of cardiologists and primary care physicians in diabetes care: "This is an important milestone—it underscores the important change we've seen in the last few years," as guidelines have changed to reflect new evidence, he said in an interview with *The American Journal of Managed Care®*. "There are now multiple options for patients with [T2D] and established cardiovascular disease, and that's critically important."

For ACC to put the cardiologist in charge of management of cardiovascular risk for a patient with T2D is a major step forward, Seck said. "Before, diabetes was about managing glucose, and the cardiologist was much less involved," he said.

The shift began in 2008, when the FDA began requiring that makers of T2D therapies conduct large cardiovascular outcomes trials to demonstrate safety (see **Cover**). Then, in September 2015, investigators for the EMPA-REG OUTCOME trial stunned the diabetes community with results that showed a 38% reduction in cardiovascular death and a 32% reduction in death from any cause, compared with placebo.[3]

Researchers also found significant reduction (35%) in hospitalization for heart failure, an area that would attract more interest as real-world data produced similar findings.[3] In December 2016, empagliflozin became the first drug to receive an FDA indication to reduce the risk of cardiovascular death for adults with T2D.[4]

In 2017, the CANVAS trial found that the SGLT2 inhibitor canagliflozin (Invokana, Janssen) reduced the risk of cardiovascular events, but that trial did find an increased risk of lower limb amputation (primarily at the toe or metatarsal),[5] and FDA requires a boxed warning on this therapy, even though it separately granted a cardiovascular indication.[6]

The cardiovascular benefit of liraglutide was seen in the LEADER trial, presented in June 2016. Results showed a 22% reduction in cardiovascular death, as well as reductions in nonfatal myocardial infarction and stroke.[7] In August 2017, the FDA approved an indication that this injectable drug can reduce 3 major cardiovascular events for patients with T2D and existing cardiovascular disease.[8]

SGLT2 inhibitors work through a unique mechanism of action that targets a protein responsible for the reuptake of glucose; as a result, the body expels excess glucose through the urine. A person with T2D can lose as much as 100 mg of glucose a day.[9] Seck said researchers are still working to fully understand this mechanism and its role in risk reduction; he pointed to the recent results from the EMPA-HEART Cardiolink-6 study presented at the American Heart Association, which found that patients taking empagliflozin for 6 months had significantly reduced left ventricle mass compared with those taking placebo, as well as reduced systolic blood pressure.[10]

The apparent ability of empagliflozin to treat patients with chronic heart failure is being explored in the EMPEROR trials, which include some patients without diabetes; whereas EMPERIAL, which will assess the effects of empagliflozin on exercise capacity in heart failure patients, will produce results sooner.[11]

Beyond the randomized clinical trials, real-world evidence from both the CVD-REAL[12] and EMPRISE[13] studies confirm what was seen in EMPA-REG OUTCOME: that SGLT2 inhibitors generally, and empagliflozin in particular, prevent hospitalization for heart failure and all-cause mortality. Although some discount the value of this data, Seck does not. This is meaningful data to prescribers, he said, and "More and more, real-world evidence can be used for regulatory decision making as well." ◆

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GUIDELINES UPDATE

New Cholesterol Guidelines Call for Personalized Care

Mary Caffrey

NEARLY 1 IN 3 AMERICANS has high levels of low-density lipoprotein (LDL), or "bad," cholesterol, but deciding on treatment requires that physicians look at each person's age, health status, family history, and other factors, according to new guidelines presented on November 10, 2018, at the American Heart Association's (AHA) 2018 Scientific Sessions in Chicago, Illinois, and published in *Circulation*.[1]

LDL cholesterol contributes to plaque buildup and narrowing of the arteries. About 94.6 million (39.7%) of American adults have total cholesterol levels of 200 mg/dL or higher. High-density, or "good," cholesterol carries excess cholesterol and carries it back to the liver, while LDL cholesterol builds up on the walls of the arteries. Evidence shows that keeping LDL cholesterol below 100 mg/dL makes a person less likely to develop heart disease or experience a stroke.[1]

Two dozen experts from the AHA and representatives from 11 other organizations weighed in on the guidelines, which call for physicians to start tracking their patients' LDL cholesterol early in life and encouraging heart-healthy diet and lifestyle behavior across the life span. In some cases, children with a family history of heart disease or high cholesterol could be screened by age 2, and children without known risk factors could be screened for the first time between ages 9 and 11 and again between ages 17 and 21.

"We think doctors ought to pay more attention to young adults," Scott M. Grundy, MD, PhD, chairman of the writing committee, said in a statement. If their cholesterol is elevated, "they might not need a statin, but they certainly need attention," he added.[2]

The new guidelines suggest patients start with statins and add other therapies if statins do not lower LDL cholesterol to safe levels. High points from the recommendations include treating patients with very high-risk atherosclerotic cardiovascular disease (ASCVD) to an LDL cholesterol threshold of 70 mg/dL; if the patient cannot achieve this target with maximally tolerated statins, physicians should consider use of ezetimibe (Zetia/Merck) or other nonstatins.

"The truth about clinical medicine is there is no black-and-white. It's all gray," said Donald Lloyd Jones, MD, cardiologist and another member of the writing committee. "That's why the emphasis in this document is [on] making sure the patient and doctor are having well-informed discussions about the benefits and potential risks of drug therapy."[2]

Lloyd-Jones said decisions are more challenging when the patient has risk factors but has not had a heart attack or a stroke and prevention is the priority. "That's when the decision is more difficult and detailed and personalized discussion is very important," he said.

Another recommendation is to incorporate the use of the risk calculator first published in 2013 by the AHA and the American College of Cardiology.[3] Other recommendations include:

- In patients with severe primary hypercholesterolemia (LDL cholesterol level ≥190 mg/dL), begin a high-intensity statin without calculating 10-year ASCVD risk.
- In those 40 to 75 years of age who have diabetes and an LDL cholesterol level ≥70 mg/dL (≥1.8 mmol/L), begin a moderate-intensity statin without calculating 10-year ASCVD risk.
- For those 40 to 75 years of age who are being evaluated for primary ASCVD prevention, shared decision making with a physician is recommended before starting statin therapy.
- For those 40 to 75 years of age without diabetes and with LDL cholesterol levels ≥70 mg/dL (≥1.8 mmol/L) and a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if discussions with a physician point to statin therapy.
- In adults 40 to 75 years of age without diabetes and a 10-year ASCVD risk of 7.5% to 19.9%, risk-enhancing factors suggest initiation of statin therapy.
- For adults 40 to 75 years of age without diabetes and with LDL cholesterol levels ≥70 to 189 mg/dL (≥1.8-4.9 mmol/L) and a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring coronary artery calcium.

The guidelines call for physicians to gauge adherence and response to therapy after 4 to 12 weeks or after adjusting the statin dose. This step should be repeated every 3 to 12 months, as often as necessary.

The guidelines also include a recommendation for a quality-and-value discussion of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which were approved to great fanfare in 2015 after results from clinical trials showed they could reduce LDL cholesterol levels by up to 60%. But list prices of more than $14,000 a year caused formulary managers to restrict access to only the most at-risk patients. In recent months, manufacturers have cut prices, after Sanofi worked out an agreement with Express Scripts (**SP617**).

Under the deal, Express Scripts will reduce prices and speed access for those who meet FDA-approved criteria of clinical ASCVD or heterozygous familial hypercholesterolemia and inability to achieve safe levels of LDL cholesterol even while taking maximally tolerated statins. In return, Sanofi's alirocumab (Praluent) will receive exclusive formulary access instead of Amgen's evolocumab (Repatha). In October, Amgen reduced prices for evolocumab as well.

"There have been concerns over the cost of PCSK9 inhibitors, and some insurance companies have been slow to cover them, so it's important to note that the economic value of these new medications may be substantial only for a very specific group of people for whom other treatments haven't worked," Ivor Benjamin, MD, FAHA, president of the AHA, said in a statement. "The association is bringing together stakeholders to discuss financial barriers to the care of heart disease and stroke. We have been heartened that drugmakers have recently agreed to reduce the prices of PSCK9 inhibitors and are making arrangements with payers to ease the financial burden for patients who could benefit from the additional medication options."[4] ◆

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Coverage by Mary Caffrey, Surabhi Dangi-Garimella, PhD, Jaime Rosenberg, Samantha DiGrande, and Kelly Davio

Boehringer Ingelheim photo

Analysis Estimates Empagliflozin Will Add Years to Life for Those With Type 2 Diabetes

RESULTS DERIVED FROM THE CARDIOVASCULAR outcomes trial for empagliflozin (EMPA-REG OUTCOME) suggest that the drug could extend life for individuals with type 2 diabetes (T2D), with greater benefits for those who start taking the drug at younger ages. The survival estimate analysis appears in the journal *Circulation*, the official journal of the American Heart Association.[1] Empagliflozin is sold as Jardiance by Boehringer-Ingelheim and Eli Lilly, which funded the study.

Using actuarial methods and assuming the benefits of empagliflozin remain constant, the team, led by Harvard biostatistician Brian Claggett, PhD, estimated that the therapy could extend life by between 1 and 4.5 years. They made their calculations based on data gathered from 7020 people who took part in EMPA-REG OUTCOME, the first trial that showed a T2D therapy was not simply safe, but also had cardiovascular benefits.[2]

The trial showed a 38% relative risk reduction in cardiovascular death and a 32% risk reduction in all-cause mortality among those with T2D and cardiovascular disease. Empagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and since the publication of EMPA-REG OUTCOME, competitors in the class have reported cardiovascular benefits.

In this new analysis, the survival benefit was greater for younger patients and diminished, compared with placebo, as the study patients aged. The mean differences between patients taking empagliflozin and those taking placebo were 4.5 years at age 45, 3.1 years at age 50, 2.5 years at age 60, 2.0 years at age 70, and 1 year at age 80.

"For a 60-year-old living with type 2 diabetes, who has already had a cardiovascular event, previous studies estimate that life expectancy could be reduced by up to 12 years compared with someone of the same age without these conditions," Claggett said in a statement.[3] "This latest analysis estimates that empagliflozin could prolong such a person's life span by, on average, 2.5 years."

The findings came as an FDA advisory committee voted 10-9 to continue large cardiovascular outcomes trials like EMPA-REG OUTCOME (See **Cover**), which were required after concerns over the safety of rosiglitazone.

A report in *Diabetes Care*, whose authors included some of the leading scientists who worked on these trials, notes that although the round of trials have revealed unanticipated benefits, the high costs involved must be considered.[4] ◆

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Cardiovascular Results for Dapagliflozin Point to SGLT2 Use to Prevent Heart Failure

RESULTS FROM THE 17,000-PATIENT cardiovascular outcomes trial for dapagliflozin, the sodium-glucose cotransporter 2 (SGLT2) inhibitor sold as Farxiga (AstraZeneca), DECLARE-TIMI 58 (Dapagliflozin Effect on CardiovascuLAR Events), presented November 10, 2018, at the American Heart Association (AHA) annual meeting in Chicago, show the type 2 diabetes (T2D) drug safely controls blood glucose, significantly reduces hospitalization for heart failure, and may slow the loss of kidney function. The drug did not produce the same mortality benefits seen with competitors in the class. Results were simultaneously published in the *New England Journal of Medicine*.[1]

The big news, however, is what heart failure specialists have wondered about for some time: that dapagliflozin, and perhaps the entire SGLT2 class, might someday be used to prevent heart failure among a much larger group of T2D patients who are at risk but have not become seriously ill. In the United States, 30 million individuals have diabetes; all but 1.25 million have T2D.[2] About 5.7 million people have heart failure, and diabetes is a leading cause. About half of those with heart failure die within 5 years of diagnosis.[3]

"The SGLT2 inhibitor benefits for heart failure and renal dysfunction were quite consistent for all populations of patients, with or without pre-existing atherosclerotic cardiovascular disease [(ASCVD)]," and with and without pre-existing heart failure or kidney disease, said lead study author Stephen D. Wiviott, MD, FACC, of Brigham and Women's Hospital, in an interview with *Evidence-Based Diabetes Management*™ prior to the AHA annual meeting.

Previous cardiovascular outcomes trials for the SGLT2 inhibitors empagliflozin (Jardiance, Eli Lilly/Boehringer Ingelheim) and canagliflozin (Invokana, Janssen) prompted the American Diabetes Association and the European Society of Cardiology to revise guidelines for patients with established cardiovascular disease. DECLARE-TIMI 58 was designed differently from those trials, however, and included more than 10,000 patients who had risk factors for ASCVD but had not developed the disease.

The results of this study offer the strongest evidence to date that treating healthier patients with T2D using SGLT2 inhibitors can prevent heart failure among those at risk for this condition, a finding that could have enormous impact on managed care. The Framingham Heart Study[4] has found that women with diabetes are 5 times more likely to develop heart failure, and men are 2.4 times more likely to develop it. Patients with heart failure are among the sickest in the health system, with total costs of $30 billion a year, according to the CDC.[3]

"These new data suggest that in patients without established atherosclerotic cardiovascular disease, SGLT2 inhibition can prevent serious clinical events, particularly hospitalization for heart failure, and possibly reduce the likelihood of progression of renal disease," Wiviott et al wrote in their findings.

A meta-analysis of the 3 major cardiovascular outcomes trials involving SGLT2 inhibitors, appearing in *The Lancet* less than an hour after presentation of the DECLARE-TIMI 58 results, found that drugs in this class appear to be producing modest results in reducing heart attacks and strokes, but "robust" outcomes in reducing hospitalization for heart failure and progression of renal disease.[5]

Under a 2008 FDA guidance, the makers of all T2D therapies were required to conduct large cardiovascular outcomes trials to ensure that the drugs did not cause heart attacks, strokes, or early cardiovascular death. The diabetes community was stunned in September 2015 when results from EMPA-REG OUTCOME[6] showed that empagliflozin was not only safe, but also produced a 38% reduction in cardiovascular deaths and a 32% reduction in deaths from any cause, in addition to a 35% reduction in hospitalization for heart failure.

Canagliflozin followed in June 2017 with results from CANVAS,[7] which found a 14% reduction in a composite outcome of reduction in death from cardiovascular causes, myocardial infarction, and stroke, but an increased risk of lower extremity amputation (primarily at the toe or metatarsal). The CANVAS results also showed a delay in loss of renal function and a reduction in hospitalization for heart failure; although the reduction was greater for those with established heart failure (39% vs 13%), CANVAS also hinted at a protective benefit[8] that should be confirmed in other trials.

"These positive results are clinically relevant to the 425 million people worldwide with diabetes, of whom those with type 2 diabete have a 2 to 5 times greater risk of heart failure along with an increaed risk of heart attack or stroke."

— Elizabeth Bjork, vice president, head of cardiovascular, renal, and metabolism, Global Medicines, Development AstraZeneca

After the EMPA-REG OUTCOME results were announced, the DECLARE-TIMI 58 investigators decided to include 2 primary efficacy outcomes: (1) major adverse cardiovascular events, or MACEs; and (2) a composite of cardiovascular death and hospitalization for heart failure. AstraZeneca had previously announced topline results for DECLARE-TIMI 58. Complete results of 17,160 patients who were followed for a median of 4.2 years found:

- Dapagliflozin was noninferior to placebo with respect to the primary safety outcome (95% CI, <1.3; P <.001 for noninferiority).
- For the first primary efficacy endpoint, dapagliflozin did not result in a lower rate of major adverse cardiovascular events (MACE) (8.8% for the MACE group vs 9.4% in the placebo group; hazard ratio [HR], 0.93; 95% CI, 0.84-1.03; P = .017).
- For the second primary efficacy endpoint, dapagliflozin resulted in a lower composite rate of cardiovascular death and hospitalization for heart failure (HHF) (4.9% vs 5.8% for placebo), for a reduction of 17% (composite HR, 0.83; 95% CI, 0.73-0.95; P = .005). This was driven by the reduction in HHF; there were no between-group differences in cardiovascular death. The HR for HHF was 0.73; 95% CI, 0.61 to 0.88).

The study authors say that, although they cannot rule out that the differences between the drugs themselves account for the lack of a mortality benefit in DECLARE-TIMI 58, they speculated that trial design may account for this, given the drug's mechanism of action. They note the trial had a "more restrictive exclusion of patients according to creatinine clearance" that could account for the difference; mortality rates were lower in the placebo group than in EMPA-REG OUTCOME, suggesting population differences.

SGLT2 inhibitors have a mechanism of action that involves blocking a protein that normally allows the body to reabsorb glucose; instead, the body discharges excess glucose through the urine, offering those with T2D glycemic control, as well as reduced blood pressure and modest weight loss. Wiviott said in the interview that besides the renal benefits, DECLARE-TIMI 58 showed no evidence of early concerns about bladder cancer—in fact, the treatment group had lower rates.

"These positive results are clinically relevant to the 425 million people worldwide living with diabetes, of whom those with type 2 diabetes have a 2 to 5 times greater risk of heart failure along with an increased risk of a heart attack or stroke. Heart failure survival rates are only 50% after 5 years from diagnosis, which is why these new findings are so important in broadening our understanding of how to go beyond blood glucose so we may better address this serious and often overlooked cardiovascular complication," said Elizabeth Bjork, vice president, head of Cardiovascular, Renal and Metabolism, Global Medicines, Development for AstraZeneca, in a statement.[9]

The FDA recently held a 2-day hearing on the future of the cardiovascular outcomes trials; these studies generated the unexpected results in EMPA-REG OUTCOME and have produced the consistent results suggesting a new way forward to prevent heart failure. Asked to reflect on the value of these trials, Wiviott said, based on the changes to clinical guidelines the trials have already produced, it would be hard to imagine a major new class of diabetes drugs reaching the market without demonstrating cardiovascular benefits.

"It will be sorted out by the clinical community and by the market, in a sense," he said. "One of my take-home messages about this whole area and what's happening is that we are really moving to a place where it's not enough to lower blood sugar—it's *how* you lower it—by choosing the right agents as opposed to simply getting to a specific hemoglobin A1C target."

When asked about the managed care benefits of using SGLT2 inhibitors, and dapagliflozin in particular, to prevent heart failure, Wiviott said that cost-benefit analyses are still needed. However, with an aging population and the prospect for more patients with diabetes and congestive heart failure, he said, "there's no question that it is important to find ways to reduce the long-term costs of these conditions."

"The concept of preventing events does have some real economic merit," he said. "Most of the heart failure drugs we use are for treating patients with established heart failure." Preventing heart failure in patients who do not realize they are at risk for the disease would be a different concept, Wiviott said.

Some heart failure specialists called for greater focus on this area a decade ago when cardiovascular outcomes trials began. They argued that the FDA should be equally focused on heart failure and not just on events like heart attacks and strokes. In an interview with *EBDM* in 2017, Brigham and Women's Eldrin F. Lewis, MD, MPH, said that with diabetes being the number 2 risk factor for heart disease, it is essential to find ways to prevent heart failure in the T2D population.[10]

"Especially in patients who have what I call the trifecta—hypertension, diabetes, and pre-existing atherosclerotic cardiovascular disease—those are very high-risk populations," he said in the interview. "Lipid lowering is important, as well, in these patients, but we need some type of precision medicine approach to managing the prevention of heart failure." ◆

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Oral Semaglutide Offers Superior A1C Reduction, Weight Loss in PIONEER 5 Trial

NOVO NORDISK ANNOUNCED in August 2018 that topline results for its phase 3a trial of oral semaglutide show the drug reduced glycated hemoglobin (A1C) and helped patients with type 2 diabetes (T2D) lose weight after 26 weeks. If successful, the drug would be the first glucagon-like peptide-1 (GLP-1) receptor agonist taken once daily as a tablet.

PIONEER 5 is one of 10 trials involving the study drug. An injectable form of semaglutide, sold as Ozempic, received FDA approval[1] last year.

Results of the PIONEER 5 trial, which involved 324 people with T2D and moderate renal impairment, showed that those treated with 14 mg oral semaglutide saw an A1C reduction of 1.1% compared with 0.1% for placebo. The group taking the study drug lost 3.7 kg compared with 1.1 kg for placebo.

From an average baseline A1C of 8%, the share of people reaching the target A1C of 7% by week 26 was greater with oral semaglutide than with placebo: 64% versus 21%, respectively. A target of 7% is recommended by the American Diabetes Association and other major diabetes professional organizations, as well as the Joslin Diabetes Center.

According to the statement[2] from Novo Nordisk, PIONEER 5 involved 2 statistical approaches:

- A primary approach required by regulatory guidance that evaluates the drug's effect, regardless of discontinuation of treatment or use of rescue medication. During the trial, 15% discontinued treatment due to adverse events, primarily nausea, compared with 6% who discontinued while taking placebo.
- A secondary approach described the effect of the drug while on treatment, without the use of rescue medication.

The population in PIONEER 5 had T2D and moderate renal impairment inadequately controlled with metformin, sulfonylurea alone or in combination with metformin, or basal insulin alone or in combination with metformin.

"The results from PIONEER 5 showed that oral semaglutide is efficacious and has a solid safety profile in people with type 2 diabetes and moderate renal impairment, thereby further expanding the solid clinical profile of oral semaglutide," said Mads Krogsgaard Thomsen, executive vice president and chief science officer, Novo Nordisk.

"Renal impairment is a serious diabetes complication and people with this condition have limited oral anti-diabetic treatment options," he said. "If approved, oral semaglutide represents an efficacious new solution." ◆

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Stricter Blood Pressure Guidelines Could Prevent Cardiovascular Events, but Debate Continues

A YEAR AGO, THE AMERICAN COLLEGE OF CARDIOLOGY (ACC) and the American Heart Association (AHA) updated new blood pressure guidelines[1] that lowered the threshold, from 140/90 mm Hg to 130/80 mm Hg, at which some patients should be treated for hypertension.

A new study, published in the AHA journal, *Circulation*, found that guideline change could translate into 3 million fewer cardiovascular disease events over 10 years, compared with earlier guidelines.[2] "Treating high blood pressure is a major public health opportunity to protect health and quality of life for tens of millions of Americans," said lead author Adam Bress, PharmD, MS, assistant professor of Population Health Sciences at University of Utah Health, in a statement.[3] "Achieving these lower goals will be challenging."

But along with commentary, Bress' study is just one among several that have come recently that show, despite a landmark National Institutes of Health (NIH) study in 2015 that seemed like a mandate for lower blood pressure targets, not everyone is on board. The new study additionally says that for the highest-risk cardiovascular patients, the new guidelines could result in an increase of treatment-related serious adverse events, which suggests the need for personalized care.

One challenge is the Western diet, which is cited as the cause of rising levels of obesity and diabetes around the world. The assumption that blood pressure must rise with age may not be true, and it may be more closely connected to what we eat.

In a study recently published[4] in *JAMA Cardiology* compared the blood pressure of 2 remote South American tribes, one which had no exposure to Western dietary patterns and the other which had some exposure to processed foods with higher levels of salt. Despite similar genetic backgrounds, the tribe that consumed saltier foods had higher blood pressure. Many believe the real key to treating heart disease and diabetes is getting serious about dietary and nutrition policy.

Bress and his team calculated fewer events in middle-aged adults based on the 2017 blood pressure goals when compared with guidelines in the seventh report of the Joint National Committee, known as JNC7, as with the eighth report of the Joint National Committee (JNC8), which put the cutoff for hypertension at 140/90 mm Hg for patients younger than 60 and 150/90 mm Hg for those aged 60 or older.

Franz H. Messerli, MD, and Sripal Bangalore, MD, MHA, writing in the *Journal of the American College of Cardiology* recently explained how physicians are justifiably confused. They offer a case study of a 63-year-old female patient with blood pressure readings that average 148/86 mm Hg. Guidelines between ACC/AHA, which cover 25,000 cardiologists, and those of the European Society of Hypertension and European Society of Cardiology, which cover 75,000 physicians, are not in alignment.[5]

ACC/AHA guidelines say her blood pressure should be 130/80 mm Hg. The European guidelines say her blood pressure should be 140/90 mm Hg. However, guidelines for the American College of Physicians and the American Association of Family Physicians say she is just fine at 150/90 mm Hg. The guidelines also do not align on how many medications to use when starting treatment.

Ironically, all 3 guidelines are based on the same study, called SPRINT (Systolic Blood Pressure Intervention Trial). This was a large trial[6] by the NIH that stopped early because it became clear that treating patients to a lower blood pressure target was resulting in fewer fatal cardiovascular events.

Despite this, the American College of Physicians and the American Association of Family Physicians guidelines insist that treating blood pressure to a target of 130/80 mm Hg across a population of older adults will result in "low-value care."

Messerli and Bangalore see more frustration ahead. "The above hypertension guideline fiasco eloquently illustrates the potential shortcomings of dogmatic clinical directives and, if anything, is prone to increase the rift between those who preach, those who teach, and those who treat," they wrote.

"Unless we make a concerted effort to do so, as the number of guidelines is increasing more rapidly than does iron-clad evidence, we are prone to see more and more schism among recommendations, confusion among physicians, and anxiety among patients," the authors concluded. ◆

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Amgen Announces 60% Reduction in List Price of PCSK9 Inhibitor Evolocumab

IN ALIGNMENT WITH the American Heart Association's Value in Healthcare Initiative, Amgen has announced that the price of its proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, evolocumab (Repatha), will be reduced by approximately 60%, from an annual price of about $14,100 down to $5850.

Evolocumab was approved in 2015[1] for use in addition to diet and maximally tolerated stain therapy in adult patients with heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, or clinical atherosclerotic cardiovascular disease, such as heart attacks or strokes, who require additional lowering of low-density lipoprotein cholesterol. Its staunch competitor, Sanofi-Regeneron's alirocumab (Praluent), was approved just a month prior to treat patients with familial hypercholesterolemia, as well as high-risk patients with demonstrated heart disease whose cholesterol has not been controlled with maximally tolerated statins.

However, the launch price of these drugs was a point of contention and debate for a while. Alirocumab also had an annual price tag of over $14,000.

An early report from the Institute for Clinical and Economic Review (ICER) proposed that the PCSK9 inhibitors should cost 85% less[2] than what they were listed at. "Our draft report suggests that $2177 is the price that should serve as an alarm bell—if the cost is more than $2177 a year, drug companies, doctors, insurers, and other parties may need to work together to determine ways to limit the use of these drugs, find savings in other parts of the health care system, or adopt other measures to help make these drugs more affordable," Steven D. Pearson, MD, MSc, the founder and president of ICER, had said about their analysis.

Earlier this year, Sanofi and Regeneron announced a deal[3] that the companies struck with pharmacy benefit manager (PBM) Express Scripts, under which alirocumab was included in the PBM's National Preferred Formulary and would cost much less than its $14,000 annual price tag for patients who purchase the drug through Express Scripts.

In a press release,[4] Amgen's chairman and CEO, Robert A. Bradway pointed out that patient out-of-pocket cost burden is a big barrier to access for the significant number of patients who suffer from cardiovascular disease, including 75% of Medicare patients who are prescribed a PCSK9 inhibitor but never fill the prescription because of the price burden. "We want to make sure that every patient who needs Repatha gets Repatha," Bradway said.

Amgen has been offering payers significant rebates on Repatha in exchange for improved patient access through tactics such as healthcare utilization management criteria. Additionally, agreements with payers representing greater than 65% of Repatha's commercial revenue are currently in place, according to the release.

"Higher rebates don't typically result in lower out-of-pocket costs for patients, especially for Medicare patients," said Murdo Gordon, executive vice president of Global Commercial Operations at Amgen. "We are confident today's action will address this challenge."

Evolocumab's original list price of $14,000 is expected to be phased out by late 2020. ◆

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Gallup-Sharecare Report Shows How Diabetes Ranks Grew Across the United States

RATES OF OBESITY AND DIABETES continue to rise at alarming rates in the United States, and a decade's worth of data show how another 1.7 million Americans were diagnosed with diabetes because the disease is becoming more common, according to a new report.[1]

The Gallup-Sharecare 2017 State and Community Rankings for the Prevalence of Diabetes, gleaned from the Gallup-Sharecare Well-Being Index, found that the overall diabetes rate increased from 10.8% nationwide in 2008 to 2009 to 11.5% in 2016 to 2017.

But distribution patterns of the disease, as well as obesity, which helps drive it, are hardly equal. According to Dan Witters, research director of the Gallup-Sharecare Well-Being Index, states and communities that had high rates of diabetes a decade ago generally still do.

In general, these states have higher rates of poverty and smoking; dietary patterns and sedentary lifestyles also contribute to rates of diabetes that top 13% and obesity rates that exceed 30% (in 2016-2017) for the 10 states with the unhealthiest profiles: Indiana, Oklahoma, Tennessee, Alabama, Arkansas, Louisiana, Kentucky, Mississippi, South Carolina, and West Virginia.

The index also breaks down diabetes and obesity rates by metropolitan statistical area, and the 10 communities with the highest rates of diabetes and obesity are: Spartanburg, South Carolina; Lakeland-Winter Haven, Florida; »

Visalia-Porterville, California; McAllen-Edinburg-Mission, Texas; Youngstown-Warren-Boardman, Ohio and Pennsylvania; Beaumont-Port Arthur, Texas; Shreveport-Bossier City, Louisiana; Ocala, Florida; Kingsport-Bristol, Tennessee and Virginia; and Fort Smith, Arkansas and Oklahoma.

Both the report and years of CDC data show the strong relationship between high obesity rates and subsequent high rates of diabetes. "About 54% of middle aged Americans who are obese and have not yet developed diabetes will do so in their lifetime," the report states. Indeed, the report found that over the past decade, obesity rates climbed in 34 states, and 15 of these states also had a corresponding rise in diabetes. "States with a rising obesity rate are about 2.3 times more likely to also be experiencing rising diabetes prevalence than are states without a rising obesity rate," the report states.

Both Witters and Sheila Holcomb, RD, LD, CDE, vice president for Sharecare, discussed the implications of these trends for the nation's healthcare system as the population ages and more Americans move into Medicare. "It was eye-popping for us," Witters said in an interview with *The American Journal of Managed Care®*. "It was more grim than what I was bracing for."

"The basic rule is for every 3% increase in obesity, there is a 1% increase in diabetes. You'll find that in the states, too. And no states have seen obesity go down." This finding is consistent with data released by the CDC that show the number of Americans with diabetes rising past 30 million in 2017, with all but 1.25 million having type 2 diabetes.[2]

Turning the tide on diabetes, as well as obesity, is going to take collaboration at the community level–from getting local leaders to provide more green spaces, to getting stores to put produce at the front of the store, to getting restaurants to put healthier items on the menu.

Holcomb said turning the tide on diabetes, as well as obesity, is going to take collaboration at the community level, from getting local leaders to provide more green spaces to getting stores to put produce at the front of the store to getting restaurants to put healthier items on the menu. Schools and workplaces will need to participate by putting healthier items in cafeterias and encouraging people to exercise. Employers will need to pay for gym memberships, she said.

When asked about the resistance former First Lady Michelle Obama encountered when she promoted healthy eating, including healthier school lunches, Holcomb acknowledged that change will come slowly. "It starts in the home," she said. "Children do whatever they are being exposed to in the home, and that's the habit they develop for the rest of their lives."

Witters said changing the culture of American food and exercise patterns will be a long-term struggle. He likened it to the public health effort to combat smoking, which began with the 1964 report to the Surgeon General and continues to this day. In the 1950s, at least half of American adults smoked; today, less than 20% do.

"You don't turn the Titanic on a dime to get those cultural shifts," he said. "It takes a generation."

The good news is some states are passing sugar and soda taxes. "We're recognizing that more of the cheap, bad-for-you junk food that's high in processed sugar is turning around and costing our society huge amounts of money down the road," Witters said.

The report profiles a pair of local health systems—Parkview Health in Fort Wayne, Indiana, and Our Lady of Lourdes Memorial Hospital in Binghamton, New York—that adapted their delivery systems for better diabetes care. Our Lady of Lourdes, in particular, has developed systems to avoid severe hypoglycemia.

Witters and Holcomb see the alarm about diabetes and obesity finally moving out of the healthcare policy and human resources domains, and reaching the level of broader public awareness.

"It has to be local community leaders and healthcare professionals developing these changes," Holcomb said. "It's not going to happen overnight." ◆

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Congress' Diabetes Caucus Seeks Transparency, Value-Based Contracts to Control Insulin Prices

VALUE-BASED CONTRACTS and alternative payment models that remove rebates are just 2 ways that policy makers could rein in skyrocketing insulin prices, according to a new report from the Congressional Diabetes Caucus, a bipartisan group that spent a year asking why prices have soared over the past decade for a hormone some patients need to stay alive.

The report came on the first day of November, which is Diabetes Awareness Month. With the report, came word that Sanofi would expand a program[1] to help reduce out-of-pocket costs for those who use insulin.

Out-of-pocket costs for insulin can exceed $600 a month, and some patients now ration insulin or skip doses. This spring, the CDC reported[2] a rise in hospitalizations from diabetic ketoacidosis, which can occur when patients miss insulin doses.

Insulin manufacturers have been under fire for more than a year over rising costs. All 3 major companies—Sanofi, Novo Nordisk, and Eli Lilly—are involved in federal litigation[3] over pricing practices, which has stalled over whether pharmacy benefit managers (PBMs) should be sued at the same time.

The Caucus, led by US Representatives Tom Reed (R-New York) and Diana DeGette (D-Colorado), reached conclusions somewhat similar to the plaintiffs in the lawsuit. In its report,[4] the group found that the current system of rebates paid to PBMs, which critics say distorts prices across a range of therapies, hits especially hard in the insulin market.

The report outlines the complex insulin delivery supply chain and an even more byzantine reimbursement system, which entices various parts of the supply chain to make more money as the cost of insulin rises. Both wholesalers and PBMs make money when insulin is sold at a price greater than its acquisition cost. But then manufacturers pay PBMs rebates to encourage access to formulary, which causes insulin prices to rise to cover that spread.

Confidentiality agreements have kept information on rebates under wraps, but the report said that data show they can amount to as much as 40%. A lawsuit filed last month by the Minnesota attorney general contained redacted information that appeared to discuss a rebate contract.

Caucus members called for capping out-of-pocket costs for prescription drugs that treat chronic conditions, because skipping medication can make the disease worse. "When patients do not adhere to their prescribed chronic condition treatment plans, they often times make unnecessary visits to the hospital, where they receive expensive care," the report states.

"Capping out-of-pocket costs for life-sustaining drugs like insulin could help patients better manage their diabetes and avoid adverse outcomes leading to unnecessary hospitalizations."

Other policy recommendations focused on breaking apart these incentives for higher pricing:

- Value-based contracts between insulin makers and PBMs would reward the supply chain for better outcomes instead of encouraging patients to skip insulin.
- Alternative payment models that remove rebates could be required in Medicare and Medicaid.

- Patient out-of-pocket costs should be linked to negotiated prices, not wholesale costs.
- Policy makers should promote the development of follow-on products by taking on patent extensions.
- Generic manufacturers should be able to make older insulins that the top 3 manufacturers have pulled off the market.
- More transparency is needed at every step, and manufacturers should be required to disclose list prices.
- Policy makers should standardize formulary appeals and limit the number of formulary changes per year.

Sanofi's announcement,[1] which is available to qualifying patients, previously offered 2 insulins at a discounted price. The revised program, available at all US pharmacies, will offer all Sanofi insulins at a set price: $99 for a 10 mL vial or $149 for a box of pens. Company officials said some patients will save up to $3000 a year.

When Sanofi launched the Insulins VALyou Savings Program program, "Our goal was to support as many uninsured and underinsured people living with diabetes as we could, and we pledged to explore how to increase affordable access in the future," said Michelle Carnahan, North America head of Diabetes and Cardiovascular, Sanofi.

"We're making good on that pledge today by expanding this program. While we are off to a good start, we know that many people continue to look for more affordable insulin options. We hope the expansion and increased awareness of this program will allow more people to benefit from it." ◆

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Cancer Surpasses CVD as Leading Cause of Death in High-Income Counties

ALTHOUGH MORTALITY FROM BOTH cancer and cardiovascular disease (CVD) has steadily decreased in recent decades, CVD mortality has decreased more rapidly, resulting in cancer surpassing CVD as the leading cause of death in high-income counties in the United States, according to a new study.[1] However, CVD is still more likely to be the leading cause of death in low-income counties.

These findings mirror state-level data, which has shown that CVD was consistently the leading cause of death in the United States from 1950 to 2014, but starting in 2000, cancer mortality surpassed heart disease mortality in 2 states: Alaska and Minnesota. By 2014, cancer became the leading cause of death in 22 states.

"Heart disease has been the primary cause of death since the shift toward chronic disease as the leading cause of death in the United States in the early 1900s," wrote the study researchers. But mortality rates have decreased, which "has been largely attributed to decreased smoking, improved awareness of diet and physical inactivity as risk factors, and better treatment of cardiovascular risk factors and acute coronary syndromes."

As this shift continues, despite increasing rates of obesity and diabetes,[2] researchers have estimated that cancer is expected to surpass CVD as the leading cause of death nationwide by 2020. Seeking to understand how this transition is occurring in regions with different levels of economic development, researchers examined US death records from 2003 to 2015 from the National Center for Health Statistics' Multiple Cause of Death mortality files.

The researchers identified a total of 32,510,810 deaths across 3143 counties. During the study period, the age- and sex-adjusted mortality rate decreased by 12% in the total population, 7% in the lowest-income counties, and 15% in the highest-income counties.

Mortality rates for heart disease decreased by 28% (30% in high-income counties vs 22% in low-income counties), and cancer mortality rates decreased by 16% (18% in high-income counties vs 11% in low-income counties). CVD was the leading cause of death in 79% of all counties in 2003 compared with 59% in 2015, and cancer was the leading cause of death in 21% of counties in 2003 compared with 41% in 2015.

The transition to cancer as the leading cause of mortality in the United States occurred earlier in high-income countries than in low-income counties and earlier for Asian Americans, Hispanics, and non-Hispanic whites than for blacks and American Indians/Alaska Natives.

Expanding on these disparities, the researchers wrote: "Our data indicate continued disparities in cardiovascular and cancer mortality between blacks and other racial/ethnic groups, even in the highest-income quintiles. Blacks had higher overall mortality than any other group."

However, the findings also suggest greater improvements for blacks than all other racial/ethnic groups for all-cause, CVD, and cancer mortality during the study period. ◆

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ADA Embraces CV Risk Calculator, Calls for Using GLP-1s Before Insulin in Type 2 Diabetes

THE GROWING CONNECTION between treatment for diabetes and management of cardiovascular risk bore more fruit December 17, 2018, with the release of the American Diabetes Association (ADA) 2019 *Standards of Medical Care in Diabetes*, which marked the first the time the chapter on cardiovascular disease management was endorsed by the American College of Cardiology (ACC).

ADA's new *Standards of Care* endorse the use of ACC's and Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator Plus, which assesses a person's 10-year ASCVD risk in people with diabetes.

A separate change updates ADA's recommendation for injectable medication in patients with type 2 diabetes (T2D): in most cases, those who need additional help lowering glucose should start with glucagon-like peptide-1 (GLP-1) receptor agonists before adding basal insulin or switching to a GLP-1/insulin combination therapy.[1]

The update comes less than a month after ADA similarly endorsed the cardiologists' new pathway for patients with T2D and ASCVD. The updated ADA standards feature new language on the role of sodium glucose co-transporter 2 (SGLT2) inhibitors and GLP-1 receptor agonists in T2D care, and the need to consider heart failure in overall diabetes care.[2]

"For prevention and management of both ASCVD and heart failure, cardiovascular risk factors should be systematically assessed at least annually in all patients with diabetes," the recommendation states. The ADA document notes that risk scores and biomarkers have been developed for secondary prevention, »

which could help identify patients who could be candidates for lipid-lowering therapies.

The changes come as the FDA weighs possible changes to practice-changing cardiovascular outcomes trials, which emerged a decade ago in the wake of concerns about the safety of some classes of glucose-lowering treatments for diabetes. Not only did these trials demonstrate that SGLT2 inhibitors and GLP-1 receptor agonists did not cause heart attacks, strokes, or cardiovascular death, but the studies showed that some treatments offered cardiovascular benefits.

More trials are under way to study additional benefits to patients with heart failure or chronic kidney disease (CKD), and the ADA recommendations address the usefulness of SGLT2 inhibitors and GLP-1 receptor agonists for patients with CKD.

The 2019 *Standards of Care* also carry forward ADA's previous statements about the need to make insulin more affordable and the recent joint statement with the European Association for the Study of Diabetes on treatment for hypertension in people with diabetes.

Additional updates discuss diabetes technology, medical nutrition, reducing therapeutic inertia, managing diabetes in overweight youth, and simplifying or scaling back medication for persons with diabetes who 65 years of age or older.

"The latest evidence-based research continues to provide critical information that can optimize treatment options and improve patient outcome and quality of life," ADA Chief Scientific, Medical and Mission Officer William T. Cefalu, MD, said in a statement, noting the importance of the collaboration with ACC and the alignment of recommendations. ◆

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Biosimilars Could Drastically Reduce the Cost of Insulin

DESPITE THE FACT THAT insulin is indispensable for approximately 100 million people with diabetes worldwide, an estimated half of those patients have no reliable supply of insulin, due in large part to cost.

A newly published study[1] in *BMJ Global Health* sought to assess the cost to produce insulin and to examine how biosimilar insulin, if manufactured on a large scale, could reduce the cost of treatment for patients with diabetes.

The investigators designed formulae for estimating competitive, but profitable, prices for biosimilar insulin using the cost of an active pharmaceutical ingredient (API) and excipients either exported from India or based on quotes from biosimilar manufacturers, the cost of formulation into vials, development and regulatory costs, and a margin for operating expenses and profit.

Given the figures available, the authors calculated an estimated cost of production per vial of $1.45 to $9.64. They then arrived at the following estimated prices for biosimilar insulin treatment (in vial presentation) per patient per year:

- Regular human insulin: $48 to $71
- Neutral protamine Hagedorn insulin: $49 to $72
- Insulin glargine: $78 to $108
- Insulin lispro: $95 to $130
- Insulin aspart: $95 to $129
- Insulin glulisine: $94 to $128
- Insulin detemir: $283 to $365
- Insulin degludec: $98 to $133

Worldwide, current prices are far higher. Given government procurement prices for these drugs in multiple nations, including the United States (where insulins are regulated as drugs and not as biologics, and where subsequent-entry products are treated as follow-ons, rather than biosimilars), prices for regular human insulin are a median of 1.2 to 1.8 times the estimated prices, and current prices of insulin glargine, insulin lispro, and insulin aspart are a median of 5.6 to 7.8, 2.7 to 3.7, and 2.6 to 3.5 times higher, respectively, than the estimated biosimilar prices.

"Comparison of estimated prices with recent government procurement prices suggests that robust competition in the human insulin and insulin analogue market would lead to sizeable savings in most countries and that current manufacturers could set significantly lower prices while still making a profit," write the study's authors.

The authors also note that prices could go even lower, as prices for APIs are falling: "Even at the low volumes currently being exported from India, the linear regression models showed an 18% yearly decrease in price for exported human insulin API and a 27% yearly decrease for insulin glargine. It would be reasonable to expect that with increasing biosimilar production, API prices will continue to fall."

The authors call for national policies, such as tenders and special incentives, to spur biosimilar competition among multiple competitors and to help generate these substantial cost savings for health systems and for patients with diabetes. ◆

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