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Evidence-Based Diabetes Management

Quality Care

Accountable Care Organizations: How to Define Quality?

Cyril Tuohy

These days, talk about "quality" factors into every discussion of healthcare. So how do the nation's 449 accountable care organizations (ACOs) and ACO-like entities sponsored by hospital systems, physicians' groups, insurers, and community organizations[1] around the country define quality?

Kelly Kelleher, MD

There's no shortage of data and metrics surrounding how effectively hospitals and doctors' groups claim to be delivering care, yet pinning down what it means to deliver quality care is difficult.

Trying to define quality may well prove elusive, as ACOs are less rooted in amending the patient experience than they are in turning industry work flows and hierarchies upside down.

"ACOs are not an attempt to change the patients, but an attempt to change the (healthcare) delivery system,"

(continued on page 256)

Technology: The Artificial Pancreas

The Next Frontier for the Artificial Pancreas: Payer Coverage

Stanton R. Mehr

Make no mistake: The holy grail in the treatment of type 1 diabetes mellitus (T1DM) is a substitute for the human pancreas—or at least a system that effectively mimics its effect on insulin production and regulation. Recent developments show that we are closing in on this technological prize, and the buzz is building not only for patients who require multiple daily insulin injections, but for clinicians as well.

Many patients will want the artificial pancreas not only for the expected improvements in glycemic control but also because it promises a new level of freedom for those tied to the rigors of multiple daily injections and glucose monitoring. Once introduced to the marketplace, the real question will be: How will health plans and insurers cover these systems for possibly large populations?

Janet Sullivan, MD

Nearer the Goal Through Multiple Methods

The US Food and Drug Administration (FDA) refers to it as the "artificial pancreas device system," of which several are under investigation.

(continued on page 257)

Policy: Effect on Payers

AMA's Obesity Declaration Could Open Door for Coverage, Treatment

Peter Page

The American Medical Association's (AMA's) Board of Delegates voted June 18, years behind the rest of the medical establishment, to classify obesity as a disease,[1] a move many believe will eventually expand what insurers pay for and medical schools teach, shrink the stigma of obesity, and add important momentum to public health initiatives.

Ted Kyle, RPh, MBA

The Board of Delegates, disregarding a committee recommendation, voted to recognize obesity as a "disease state with multiple aspects requiring a range of interventions to advance obesity treatment and prevention."[1] The resolution supporting the AMA policy noted that the World Health Organization (WHO),[2] Internal Revenue Service (IRS),[3] the US Food and Drug Administration (FDA),[4] American Association of Clinical Endocrinologists (AACE)[5] and the National Institutes of Health (NIH)[6] already regard obesity as a disease.

"Recognizing obesity as a disease will help change the way the medical community tackles this complex issue that affects approximately 1 in 3 Ameri-

(continued on page 259)

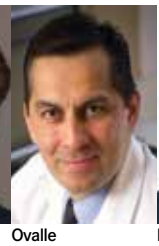
Can Restorative Yoga Trim Fat?

A study presented at the American Diabetes Association June meeting found that restorative yoga helped overweight women reduce subcutaneous fat.

See page SP 246.

Also in this issue...

Stanhope



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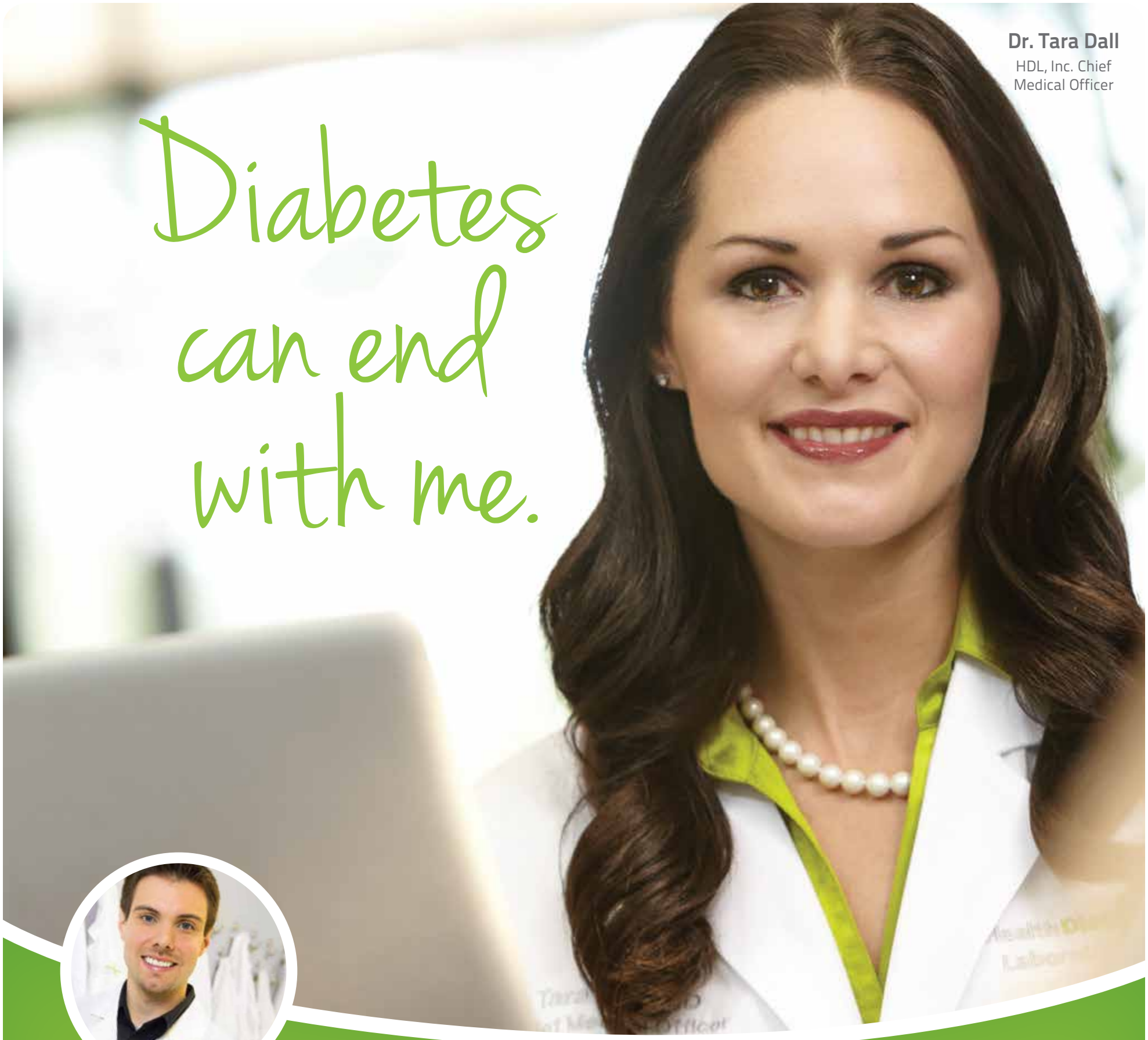

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From the Publisher

In June, members of the American Medical Association's House of Delegates voted to classify obesity as a disease, a move that will open doors for new ways to battle this epidemic. Physicians who voted did so to give primary care doctors every tool in the arsenal, including prescription drugs, even if they were not specifically mentioned in the resolution. Rather, the statement said, "There are hormonal and metabolic abnormalities not reversible by lifestyle interventions that will likely require multiple different risk stratified interventions for patients." The September issue of *Evidence-Based Diabetes Management* examines what the AMA vote means for payers, who must now respond to the obesity declaration and determine what they will fund, while ramping up to meet the requirements of healthcare reform.

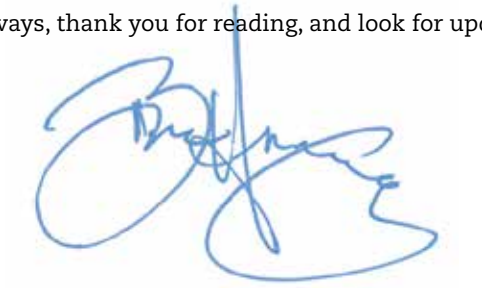
> *"There are hormonal and metabolic abnormalities not reversible by lifestyle interventions that will likely require multiple different risk stratified interventions for patients."*
>
> - American Medical Association

In the wake of the AMA's annoucement, news reports speculated that patients would gain greater access to agents that treat obesity, while drugs that await approval from the US Food and Drug Administration would gain priority. Treating obesity as a disease would give clinicians another way to attack what often results, diabetes. Fortunately, as discussions at the June meeting of the American Diabetes Association (ADA) in Chicago showed, doctors and patients have new and improved therapies in their arsenal against this chronic condition.

In just a few years, those fighting diabetes have come a long way from where we were in 2010, when the community was reeling from the FDA's action over Avandia (rosiglitazone). In this issue, *Evidence-Based Diabetes Management* takes a look back at that saga through the eyes of a former FDA regulator and a clinician on the front lines. The lessons learned affect the way FDA does business today, and, hopefully, have improved the way trials occur for the benefit of patients. Fortunately, according to Fernando Ovalle MD, the development of new classes of therapies, such as SGLT-2 inhibitors, has allowed clinicians to forward.

Some of you joined us at our live meeting ahead of the ADA sessions in June. Our next meeting will be April 10-11, at the Princeton Marriott at Forrestal, closer to our home office in Plainsboro, NJ. You will see program and registration information in upcoming issues.

As always, thank you for reading, and look for updates on www.ajmc.com.



Brian Haug
Publisher

EDITORIAL MISSION

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

In This Issue...

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Improving Patient-Centered Care in Diabetes With Comparative Effectiveness Research

Douglas K. Owens, MD, Wade Aubry, MD, Roy Beck, MD, Joshua Benner, MD, Jan E. Berger, PharmD, Michael E. Chernew, PhD, Felicia Forma, BS, Dana P. Goldman, PhD, William H. Herman, MD, Rebecca Killion, MA, Darius Lakdawalla, PhD, and Anne L. Peters, MD

The complexity of glycemic management in type 2 diabetes mellitus (T2DM) has increased dramatically in the past 15 years. In 1995, the drugs available for treatment of T2DM were insulin and sulfonylureas. Since then, 9 new drug classes have become available, significantly increasing the number of clinical options for physicians and patients. The expanded treatment options currently available, in turn, have produced more opportunities for individualized, patient-centered treatment approaches, while creating additional challenges. For example, among T2DM patients, there is substantial heterogeneity in clinical outcomes and patient preferences regarding which health outcomes and treatment effects matter to them most. For the physician who seeks an approach that maximizes an individual patient's likelihood of responding favorably to treatment while optimizing other considerations (eg, quality of life, functional ability, healthcare spending), the challenge is made greater by an insufficient evidence base to inform clinical decision making.

At a minimum, such an evidence base would include data on the comparative effectiveness of various treatment options—both overall and for specific subgroups of patients—as well as data on patient preferences that drive treatment decisions and, often, health outcomes.

Comparative effectiveness research (CER) plays an important role in generating evidence for patients, physicians, and payers; it is increasingly conspicuous in discussions about optimizing patient-centered care for T2DM. CER compares the benefits and harms of alternative treatment options to determine "what works best for which patients under what circumstances."[1] By also assessing utilization and costs, CER can provide a foundation for cost-effectiveness analysis,[2] an important approach for identifying high-value health care.[3]

The hallmark of CER is the comparison of clinically relevant alternative diagnostic or management strategies in representative clinical practice populations. With its multiple treatment alternatives and heterogeneity of patient outcomes, T2DM management is well-suited to this type of research. Accordingly, CER is increasingly used within the diabetes arena. For example, a form of CER was used to evaluate available drug therapies for T2DM.[4] However, without an economic evaluation or measurement of comparative clinical effectiveness in real-world settings, the findings are limited. In another example, a major pharmaceutical company developed its phase III clinical trials program using CER. Drawing on insights of an expert panel, the company developed a clinical research approach to provide clinical and economic data once the trials were completed, with a particular focus on enhancing liraglutide's entry into the market and integration into formularies.[5] Finally, a recent comprehensive review of randomized control trials (RCTs) and observational studies by the Agency for Healthcare Research and Quality (AHRQ) identified several gaps in the evidence on the effectiveness of oral agents for T2DM. These gaps will limit clinicians in providing patient-centered care.[6,7]

Comparative Effectiveness Research Working Group

To better understand how CER may be used to help improve patient-centered T2DM care, we convened a multidisciplinary working group that included patient representatives as well as a range of experts in: diabetes care, technology assessment, pharmacology, health economics, evidence synthesis, systematic reviews, clinical decision making, guideline development, epidemiology, clinical trials, and public policy. The group considered the following questions:

1. What are the limitations in the available evidence for patient-centered T2DM care in diabetes?
2. What outcomes are important to patients and, therefore, should be included in studies of diabetes management?
3. How should RCTs be modified to improve the evidence base for patient-centered care?
4. How should observational studies be designed to improve the evidence base for patient-centered care?

The working group made recommendations, by consensus, for how CER could be used to improve the evidence base for patient-centered diabetes care in order to make results of future diabetes management studies more useful. The final recommendations are summarized here.

The hallmark of CER is the comparison of clinically relevant alternative diagnostic or management strategies in representative clinical practice populations. With its multiple treatment alternatives and heterogeneity of patient outcomes, type 2 diabetes mellitus management is well-suited to this type of research.

Limitations of the Evidence Base for Patient-Centered Diabetes Care

The working group highlighted 5 gaps in the evidence base for T2DM patient-centered care: (1) limited evidence on long-term and patient-reported outcomes; (2) the nonrepresentativeness of patient populations and clinical settings—particularly in clinical trials; (3) the dearth of systematic data on patient subgroups; (4) the insufficient attention paid to social, cultural, and economic factors that influence care; and (5) the comparatively few direct comparisons among alternative treatment strategies. We discuss each in turn.

Limited Evidence Regarding Long-Term and Patient-Reported Outcomes

The comparatively little evidence on long-term outcomes is striking: many outcomes important to clinicians and patients are not tracked or reported. The AHRQ review, for example, found insufficient evidence to conclude that alternative T2DM treatments result in improvements in total mortality, cardiovascular mortality or morbidity.[6,7] No study in the AHRQ analysis addressed retinopathy. Only 3 studies evaluated neuropathy, and these had significant methodological flaws.[6,7] The working group also noted a lack of postmarketing surveillance, which limits the likelihood of identifying adverse events.

Another limitation of the available evidence identified by the working group is the comparatively little attention paid to results that patients find most important, which we call "patient-centered outcomes." The working group highlighted the importance of outcomes such as satisfaction with care, functional ability, and quality of life. Other outcomes that may be significant to patients include therapeutic side effects (such as weight gain and hypoglycemia), convenience, and cost. Patient-centered outcomes are important because they can influence adherence to care, among other things. Adherence is particularly challenging when patients may not fully believe in the value of the prescribed medications or if they find the regimens difficult to follow. To prevent long-term complications, diabetes care also often includes treating patients who are asymptomatic.

Nonrepresentativeness of Patient Populations and Clinical Settings

It is well understood that for purposes of methodological rigor, statistical power, and regulatory requirements, randomized controlled trials frequently are conducted with highly selective patient samples. For example, patients with a variety of comorbidities, poor

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Table 1. Summary of Recommendations

Recommendation	Examples of application in diabetes
Include short- and long-term outcomes relevant to patients	Mortality, cardiovascular mortality or events, stroke, cancer, ophthalmologic disease, and osteoporosis
Collect patient-centered outcomes	Satisfaction with care, quality of life, adverse events such as hypoglycemia, barriers to achieving care, adherence, persistence, required doses, and A1C targets
RCTs should compare clinically relevant alternatives	Another oral antidiabetic agents vs another oral antidiabetic agents; combination therapy regimens vs monotherapy regimens
RCTs should include patients who are representative of those seen in clinical practice	Patients who have comorbidities, or cultural barriers to care; patients who are older or socioeconomically disadvantaged; patients who are susceptible to adverse events
Develop enhanced patient registries	Measures of glycemic control; A1C targets; patient characteristics; comorbidities; patient-reported outcomes such as hypoglycemia, quality of life, and satisfaction with care
Design better observational studies by applying statistical and econometric methods to control for confounding variables	Marginal structural models, quasi-experimental designs, instrumental variable approaches can address issues with selection bias

A1C indicates glycated hemoglobin; RCT, randomized controlled trial.

adherence, or limited access to healthcare often are ineligible for clinical trials. Yet these are the patients most likely to pose management challenges in a clinical setting. Among the 166 studies examined by AHRQ, information was insufficient on patients with varying levels of cardiovascular and renal risk, with comorbid conditions, and the elderly.[7] Finally, few studies report the recruitment methods used, making it impossible to judge how representative the trial population is likely to be. For example, trials that recruit from large urban teaching hospitals might cover different patient populations than trials based in community clinics. In addition, trials that recruit through physicians might draw different patients than those recruiting using more direct methods to access patients. It is often difficult to know how these various approaches affect the sample-frame of the study.

There is also wide agreement regarding the comparative "artificiality" of clinical trial settings. In terms of a more specific gap in the evidence base for T2DM care, a concern raised by the working group is the vigilant monitoring, support, and follow-up patients receive in a clinical trial compared with the reality of the "real-world" setting, which may contribute to differences in the effectiveness of a given therapeutic intervention. Furthermore, few trials report the study settings, which makes it difficult to assess how the results apply to individual practices.[7]

Dearth of Systematic Data on Patient Subgroups

Clinical trial participants always vary in terms of demographics, comorbidities, disease states, and other potentially significant dimensions. When the variation in treatment response is substantial in a trial, the overall result might not be applicable to all enrolled patients. Yet trials often are not large enough to permit meaningful analyses of subgroups.[8] Pooling data from subgroup analyses is one way to overcome this limitation.[9] Such research underscores the importance of assessing and reporting results of therapies in clinically important subgroups, in part to enable pooling of subgroup results from different studies.

Increasingly, large health plan databases allow for rudimentary comparisons of outcomes and costs.[10-12] These analyses can serve as hypothesis-generating tools for more detailed economic and clinical analyses of best practices for patient care. For example, Onur and colleagues used a large commercial US healthcare data source to study the effectiveness of adding rapid-acting insulin to basal insulin therapy (with or without concomitant oral agent therapy).[13] Both overall and diabetes-related healthcare costs were reduced. These results suggest that rapid-acting insulin in this population can improve glycemia and perhaps health, but meaningful numbers are small, rates of hypoglycemia unknown, and optimal patterns for dosing and administering rapid-acting insulin unknown.

Insufficient Attention Paid to Social, Cultural, and Economic Factors That Influence Care

Differences in education, patient-physician relationships, income, and cultural norms can all influence patient management, but are not often addressed in RCTs or observational studies. Treatment plans, for example, must account for such cultural and social factors as food insecurity, economic hardship, or even the celebratory role of food in many cultures. Beliefs about alternative approaches to health (use of herbal products and supplements) also should be considered.

Comparatively Few Direct Comparisons Among Alternative Treatment Strategies

Finally, the working group noted that, in view of the vast number of treatment alternatives now available, there are a number of important comparisons among alternative treatments that have not been systematically examined to date.[7] For example, there are few good studies of comparative effectiveness and safety of 2 drug combinations or of monotherapy and combination therapy involving meglitinides, dipeptidyl peptidase-4 (DPP-IV) inhibitors, and glucagon-like peptide-1 agonists with other first-line diabetes medications. There are also few comparisons with a basal or premixed insulin added to metformin or thiazolidinediones.[7] The absence of some key treatment comparisons limits the ability of clinicians to determine the best treatment alternative for patients and to provide patient-centered care. However, the working group recognized that even if head-to-head trials were available, care for specific patients must be individualized.

Key Recommendations

The problems identified above present important challenges for the provision of patient-centered care for patients with diabetes. The following recommendations **(Table 1)** are viewed by this working group as essential for improving the relevance of RCTs and observational studies to the accumulating evidence base for patient-centered diabetes management. The recommendations are consistent with the Institute of Medicine's report on comparative effectiveness.[1] Furthermore, many of the areas identified by the group could be addressed by the newly created Patient Centered Outcomes Research Institute (PCORI), as well as by experts in academia and the private sector who conduct this type of research.

Recommendation 1. Outcome measures in research on the management of T2DM should include long-term health outcomes and other patient-reported outcomes.

Many current trials focus on intermediate end points, primarily glucose control, and fail to provide direct evidence of clinical outcomes such as mortality, morbidity, complications, and adverse effects of treatment. The working group affirmed the importance of long-term outcomes, including mortality, cardiovascular mortality, stroke, cancer, and osteoporosis, while acknowledging the difficulty of ascertaining these long-term outcomes owing to the length of follow-up, sample sizes required, costs, and because the effect of therapy early in the course of disease will be confounded by the effect of therapy later in disease.

The working group also emphasized that, to the extent possible, patient-centered outcomes should be included both in randomized trials and observational studies. For example, anxiety about hypoglycemic episodes may be an important barrier for many patients. Trials should include measures of adherence and persistence with treatment, as these are key considerations in successful patient-centered care. Finally, studies should report the goals of therapy, given that success should be assessed relative both to the targets and the adverse events associated with therapy.

Recommendation 2. Randomized control trials used in comparative effective research should be designed with the key decision-makers and objectives in mind.

Because the goal of comparative effectiveness is to help consumers, clinicians, purchasers, and policy makers make informed decisions, it is important that there be trials specifically designed to compare treatments and outcomes that are important to these groups. This includes, for example, trials which compare clinically relevant alternatives (eg, active comparators in appropriate doses) rather than an active treatment with a placebo or an alternative that is ineffective or unlikely to be used clinically.

The working group noted that trials should also include patients who are representative of those seen in clinical practice. Many trials are designed to minimize potential confounding factors

(eg, comorbid conditions) through the use of strict inclusion/exclusion criteria and selective samples. Consider the result, however: those patients with T2DM and comorbidities who are most likely to be excluded from clinical trials are typically older and more likely to be socioeconomically disadvantaged. It is important that these patients be included in trials when feasible to increase the trials' relevance to the treated population.[7]

RCTs designed in accordance with these recommendations have been called pragmatic, or practical, clinical trials.[14,15] Such trials are designed to show whether management strategies work in conditions that resemble, as much as possible, actual practice. In contrast, many current RCTs aim to determine the benefit of an intervention under "ideal" circumstances and often are performed to satisfy approval requirements of the US Food and Drug Administration (FDA).[14] As Sox and Greenfield note, such trials often ask what works, rather than which therapy works best compared with other therapies.[16] Clearly, there is a need for both types of studies.

Recommendation 3. Enhanced patient registries could serve as a basis for observational studies.

Observational studies follow patients as they are provided care in more typical clinical settings. They can play an important complementary role in CER in diabetes. They are often useful for identifying potential harms. The advantages of well-designed observational studies include the ability to assess the applicability of evidence derived through RCTs, assess how treatment is used in practice, study populations and subpopulations not studied in clinical trials, and provide long-term follow-up for large numbers of patients.[17]

Referencing these advantages, the working group recommended enhanced patient registries that could serve as the basis for observational studies. These registries would combine administrative data, laboratory data, relevant clinical data from medical records, and hemoglobin A1C targets, with patient-reported outcomes such as hypoglycemia, quality of life, and satisfaction with care. Such registries could build on the traditional strengths of observational studies while addressing some of their limitations.

Some designs and analytic approaches are more effective than others in controlling for confounds often found in observational studies. Relatively new statistical methods, such as marginal structural models, for example, are designed to reduce inferential errors that result from confounding.[18] These methods assume that potential confounders are observable. In light of this, an important aspect of enhanced patient registries is that they include sufficient clinical detail to capture the patient characteristics (eg, comorbid conditions) that influence both the choice of therapy and the outcomes of interest. In addition, some observational study designs (quasi-experimental designs, instrumental variable approaches) can control for confounding even if the confounders are not observable.[19]

The use of comparative effectiveness observational studies based on enhanced registries would have several advantages. First, they would include patients more representative of clinical practice. Second, they would enable investigators to assess adherence to treatment regimens under real-world conditions in patients with varying socioeconomic, educational, and cultural backgrounds. Finally, these studies could track patient-centered outcomes over much longer time periods than is feasible in RCTs.

The ease of conducting observational studies will increase as the use of electronic medical records increases. For example, a recent study discovered a previously unknown drug interaction between paroxetine and pravastatin that raised glucose levels. The researchers analyzed the FDA's adverse event reporting system for side-effect profiles, and then assessed glucose levels in patients receiving both medications in three populations via electronic medical records.[20] Such a study would have been impossible even in the recent past.

Conclusions

To provide patient-centered care, clinicians must identify the outcomes important to patients and understand how different therapies affect those outcomes. Despite many RCTs and observational studies that have been conducted on diabetes management, there are major gaps in the evidence that limit clinicians' ability to provide patient-centered care. These gaps exist in part because RCTs are designed for regulatory purposes or to demonstrate causality and the safety and efficacy of an intervention under "ideal" circumstances. As a consequence, important outcomes are not always addressed, the patient populations and settings may be nonrepresentative, subgroup differences on the outcome measures of interest are not well reported, and direct comparisons among treatment alternatives are lacking. These gaps can be addressed by some minor modifications to the outcome measures utilized in RCTs, the use of enhanced patient registries that can serve as the foundation for high-quality observational studies, and reliance on quasi-experimental designs for observational studies.

A large trial funded by the National Institutes of Health (NIH), The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE), should provide helpful information on how to best choose pharmacologic treatments for the management of T2DM. It is a multicenter RCT among patients with recent onset T2DM. It will compare glimepiride, sitagliptin, liraglutide, and glargine as add-on therapy to metformin. The trial has been designed following principles of CER and will seek to collect information on healthcare use, patient preferences, and quality of life. The results should help guide patients, clinicians, pharmacists, and health plan administrators in the best treatment approaches for T2DM.

The aim of our recommendations is to facilitate the development of evidence that can inform patient-centered decision making. We also highlight these issues because PCORI is setting an agenda for patient-centered outcomes research. Implementing the above recommendations would lead to improved representativeness of patients and care settings and better evidence about the real-world outcomes from alternative treatment choices. In turn, studies that more comprehensively capture patient-centered outcomes will better inform clinical guidelines for care. **EBDM**

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FDA "Mea Culpa" Part of a Cautionary Tale in Avandia Saga

Tracey L. Regan

Three years after the once-popular diabetes drug Avandia (rosiglitazone) largely disappeared from medicine cabinets following a dramatic reappraisal of its cardiovascular risk, the drug's partial vindication on June 6, 2013, by a US Food and Drug Administration (FDA) advisory panel[1] has come too late to revive its fortunes, experts say.

But the controversy that engulfed Avandia and its roller coaster ride through the regulatory process continue to have far-reaching implications for clinical practice and drug development.

"Now that the water has cleared, we look back and see that it never was a problem. There was no cardiovascular benefit, but no problem either," said Fernando Ovalle, MD, director of the Multidisciplinary Comprehensive Diabetes Clinic at the University of Alabama-Birmingham.

Ovalle was referring to the findings of an independent team of researchers from the Duke Clinical Research Institute commissioned by the FDA to analyze, or readjudicate, data from drug maker GlaxoSmithKline's RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes) trial. The Duke team concluded that Avandia did not present a serious cardiovascular risk to diabetes patients, although it pointed out flaws in the trial's design, noting that its unblinded nature could have affected the outcome. Based on that readjudication, the FDA panel voted in June to ease the tight restrictions on the drug put in place by the agency in 2010 and 2011.[2,3]

"This has put the FDA in something of a bad spot, because the agency can't really admit it was wrong, although that is what the advisory panel said," Ovalle noted.

But Ovalle, who stopped prescribing the drug more than 2 years ago, said the findings have come too late to sway public opinion.

"Avandia's reputation has been irreparably damaged," he said.

The drug's maker, GlaxoSmithKline, awaits a final ruling from the FDA, but does not plan to relaunch it in the United States.

"There is no news yet from the FDA, and so nothing's changed since the adcom (advisory committee) meeting in June. The committee's recommendations were not definitive, and the FDA takes them under advisement, and so we're in a holding pattern," said company spokeswoman Heidi Siegel, adding, however, "There are no plans to promote it again in the US."

But the readjudication was not pointless, some FDA observers say. Rather, it provided a forum for the agency to scrutinize its own practices, while furthering public debate on wide-ranging issues related to drug review and development.

"The review was done not so much to save or damn the drug, but rather to have a thoughtful look back at what happened, recognizing that the way the saga unfolded had negative effects on the environment in which drugs are developed," said G. Alexander Fleming, MD, the president and CEO of healthcare consulting firm Kinexum and a former FDA regulator who led the review of metabolic therapies such as Metformin. "And I think the agency's objective was accomplished: to air the process warts and all, and to demonstrate that the FDA has a responsibility to be data-driven."

Fernando Ovalle, MD

He added, however, "In part, the review and hearing also reflect the FDA saying 'mea culpa' for stopping a head-to-head comparison trial of Avandia and Actos. based on the Agency's safety concerns about Avandia. At the recent hearing, FDA acknowledged that the trial probably was justified and the results would have been valuable." Actos (pioglitazone), manufactured by Takeda Pharmaceuticals, was Avandia's leading competitor at the time.

Ovalle still vividly recalls Avandia's promising debut in 1999 and its subsequent fall from grace a decade later, saying the dramatic turn of events was "hard to believe" at the time.

"The drug took off. It was one of the few agents available to type 2 diabetes (T2DM) patients, and we liked the effect it had on glucose for people who had never had it under control," he said, adding, "There was some concern early on about possible liver toxicity, given the history of Rezulin—a similar drug—at that time, so we did liver exams every 3 months, but we didn't find anything and we were very happy about that. In fact, we kind of fell in love with it."

The drug was an important tool in states with high diabetes rates, such as Alabama, where 11.1% of adults were diagnosed with the disease in 2010, putting the state second only to Mississippi, with a rate of 11.3%, according to data from the Centers for Disease Control and Prevention (CDC).[4] In a class of drugs called thiazolidinediones, or TZDs, Avandia works as an insulin sensitizer, reducing the body's resistance to insulin.

Ovalle said clinicians had some new concerns about the drug after a few years, noting that some of their patients gained weight and developed problems with edema. A few ended up in the hospital, although he said that was rare.

"We still defended the drug because there was nothing like it that improved glucose numbers the way it did. In terms of cardiovascular risk, we saw LDL numbers go up a little bit, and so we said we'd watch that closely," he recalled. "On the other hand, small studies of Avandia and Actos, another TZD insulin sensitizer, showed signs of improvement as well—cardiovascular benefits in all markers except LDL, from blood pressure, to inflammatory markers, to C-reactive protein—and so it looked like these drugs were going to lower cardiovascular events significantly. But then the studies turned out negative, showing no effect. It was disappointing to learn there were no benefits, but there weren't clear bad effects either."

> *"The drug took off. It was one of the few agents available to type 2 diabetes (T2DM) patients, and we liked the effect it had on glucose for people who had never had it under control."*
>
> **—Fernando Ovalle, MD**

He added that most physicians believed that it would be hard for these drugs to show definitive beneficial effect from a cardiovascular perspective given that statins were of proven benefit and standard of care therapy, and had to be given to patients during clinical trials.

Despite some of these uncertainties, however, he said clinicians were stunned in 2007 when Steven Nissen, MD, chairman of the department of cardiovascular medicine at the Cleveland Clinic, published in *The New England Journal of Medicine* the results of a meta-analysis of Avandia trial data that showed a 43%

increase in heart attacks for those taking the drug.[5] Three years later after Nissen's report, the FDA announced it would restrict use of Avandia to patients unable to control their diabetes on other medications, ultimately requiring them to enroll in the agency's Risk Evaluation and Mitigation Strategy program in order to receive it.[2,3]

"Steve Nissen's paper came as a complete surprise to many of us who thought the opposite. He said the drug caused heart attacks. And while the medical community was given the impression with his meta-analysis that the drug was dangerous, to be fair, the meta-analysis was incomplete and heavily criticized by statisticians, but that didn't matter in the ensuing public controversy. Things became politicized, and the debate was no longer based on science," he recalled. "The FDA responded by making the 'safe' move in sharply restricting Avandia and that killed the drug. The perception was so poor that patients were asking to be taken off it. As a doctor, if you tried to reassure them, you put yourself in a bad position. Lawyers were out there advertising, saying, 'If you took Avandia, call us.' I stopped prescribing it."

Fleming described Avandia's situation as "almost unique along the spectrum of what happens in drug development and regulation."

Nissen took a look at the publically available Avandia trial data and added up the cardiovascular events associated with Avandia and the control treatment. This approach is called a meta-analysis and is generally regarded as "hypothesis-generating, never definitive because of some significant limitations," Fleming said. "There was nothing wrong with Nissen performing the meta-analysis or even the Journal publishing it, though it rarely publishes meta-analyses. The problem was with Nissen's over-reaching conclusions and the editors allowing the title of the article itself, which implied both definitiveness and that higher death rates were caused by Avandia," he said. "Nissen went on to publish conclusions that the closely related and competing drug, pioglitazone (Actos), provided cardiovascular benefits, making Avandia even more untenable."

Multiple FDA advisory panels were called—including one the resulted in the FDA "guidance," published in record time, that cardiovascular safety trials would have to be completed before any therapy for T2DM could be approved. This requirement suddenly added years and perhaps as much as $500 million to the cost of developing a drug for T2DM, Fleming said.. The controversy around Avandia itself escalated. In the wake of the Nissen paper, at FDA there was a storm of additional reviews and different opinions reached about Avandia. "In the FDA drug review process, data, analyses, and interpretations are verified by a host of well-qualified professionals. The FDA reviews of Avandia went beyond this standard approval process. It added not 1 but 2 rounds of adjudicating which patients in the Avandia RECORD trial had serious cardiovascular events. Event adjudication is generally the responsibility of an expert panel independent of the FDA and the company (though the company selects the panel). Adjudication during the initial review process may be done when there is a particular reason. What is more unusual is to have the adjudication process come after the drug approval. Even rarer, if not unique, is to have a second adjudication process as occurred with FDA's commissioning of the Duke Clinical Research Institute. The Duke report absolved Avandia from showing increased cardiovascular risk in the RECORD trial. This undoubtedly led to FDA's soul-searching." he said.

G. Alexander Fleming, MD

Since then, however, new health concerns about the entire class of TZDs have emerged, making the debate over cardiovascular risk essentially a moot point. "There is an even larger story about this class: it's going away and not because of the CV issue. Over the past several years, data have emerged that point to increased risks of bladder cancer and osteoporosis associated with pioglitazone and ongoing concern about fluid retention caused by TZDs, which could worsen congestive heart failure, TZDs have already been removed from the market in Germany and France," Fleming said.

"Over the past decade there has been a lot of progress on the drug review and the clinical development process. One of the key lessons learned is that long-term clinical outcomes do need to be verified and not just assumed. Rather than just relying on treating a number such as blood sugar, we now more often look at the longer term measure of a drug in preventing complications of the disease," he said.

"We won't see TZDs any more, although perhaps for the wrong reasons," Ovalle commented. "They are gone and we have moved on."

He said that TZDs have been replaced by new drugs that are working well, including GLP-1 (glucagon-like peptide-1) receptor agonists, DPP-IV (dipeptidyl peptidase IV) inhibitors, and most recently, SGLT-2 (sodium-glucose transport 2) inhibitors, "with no weight gain or edema, and no bad press." The new drugs accomplish some of what the insulin sensitizers did but through different mechanisms, he noted, including through weight loss.

"GLP-1 agonists are drugs that are focused on anti-hyperglycemia, and a nice side effect is that they help people lose weight. Another class of drugs, SGLT-2 inhibitors, also look like good drugs but these are new and we always have to be careful with new drugs as there may be things we don't know about them yet," he said. "In general, when I prescribe a newer drug like any of these, I now say to patients that I think it's a safe drug, but I now have to include a disclaimer on the possibility of yet unknown side effects. That's something I never did before."

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>
> **—G. Alexander Fleming, MD**

Ovalle said that Avandia's dramatic regulatory reversal, among other controversies in recent years, has left him with a somewhat jaundiced view of the agency's review process.

"I think the FDA is heavily influenced by the media. Regulators probably feel under pressure to protect their jobs," he said. "On the other hand, people who sit on the FDA's advisory panels often have close ties to the pharmaceutical industry and to particular drugs, and disclosure of these conflicts of interest is probably not sufficient."

Fleming described the controversy's legacy as mixed.

The controversy over Avandia, he said, led directly to diabetes drugs having to undergo cardiovascular safety trials. "This is not necessarily a bad idea, but it's expensive and adds 3 to 4 more years to the drug review. However, the question remains: Should this be a slavish requirement? If no other drug in the class has shown a problem, it's probably not a good idea, not just from the standpoint of cost but in terms of consuming patients who are a scarce resource. Drug companies can afford to do the trial, but they are tapping out a resource that is under pressure. The negative effect of that may be that important trials are suffering from competition for this resource from trials that are not important and take a substantial amount of time to process."

By contrast, he noted, anti-obesity drugs have not been required to do cardiovascular safety trials. "They are done on a case-by-case basis for cause. With type 2 diabetes drugs, we are headed in that direction, but it's unclear how quickly."

"Going forward, I think we need to look to a stepwise process, which should be formalized by the agency, in which products make it out of review sooner but under more restrictive use. We shouldn't have a one-size-fits-all approach or set the bar so high that it impedes development of important therapies."

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THE AMERICAN JOURNAL OF MANAGED CARE®

Rhetoric Versus Reality: Promise of 'Patient-Centered' Focus in Health Reform Missing in Endocrinology Training, Compensation

An Interview with George Grunberger, MD, FACP, FACE

A decade ago, a landmark report by Robert Rizza, MD, and colleagues found there was a 12% shortage of endocrinologists in the United States and that the shortage would grow; the study attempted to gauge workforce needs through 2020.[1] While the report was correct in stating there was a growing need, its estimates failed to gauge how rapidly the epidemics of obesity and diabetics would escalate over the next decade, leaving practicing endocrinologists more overworked than ever.

Shortages became acute, and wait times in most parts of the country would be measured in months, not weeks.[2] By January of 2013, the American Diabetes Association (ADA) and the American Academy of Pediatrics (AAP) issued updated guidelines for handling the crisis, including an emphasis on the need for better education on how to diagnose diabetes in children.[3] Among the concerns, "In 2011, 3 states had no pediatric endocrinologists, and 22 had fewer than 10, and the situation is not likely to improve in the near future."[3] Estimates of 5000 practicing endocrinologists, compared with 26 million Americans with diabetes and 79 million with prediabetes, show the math just doesn't work.[4]

With open enrollment under the Affordable Care Act (ACA) set to begin October 1, 2013, and Medicaid poised to expand in as many as 31 states,[5] new waves of patients needing an endocrinologist's care threaten to swamp an overwhelmed system. Yet the promise of health care reform, with its emphasis on quality of care instead of procedure-based rewards, would purport to signal a new era for endocrinologists, a cognitive specialty that demands patience in dealing with patients who may not listen or may experience bad outcomes despite a doctor's best efforts.

Most reports on the endocrinologist shortage have cited pay as the major factor in the crisis. A 2011 Medscape/WebMD survey found that most full-time practicing endocrinologists earned between $150,000 and $175,000 in 2010,[6] but this may not fully reflect a change in billing policy imposed that year by the Centers for Medicare & Medicaid Services (CMS).

According to George Grunberger, MD, FACP, FACE, a leader in the field and current vice president of the American Association of Clinical Endocrinologists (AACE), the rhetoric of healthcare reform is not being matched by reality for those practicing in the field. The followed interview with Grunberger has been edited and condensed for *Evidence-Based Diabetes Management*.

EBDM: **There was a major paper by Robert Rizza, MD, and others in 2003 predicting this shortage, and an update in 2008. How bad is the problem?**

Grunberger: They understated how bad the problem would be. Now, there is consternation that it was understated. It's a lot worse than people predicted back then.

EBDM: **The promise of health reform—to reward improving the health of populations through accountable care organizations, or ACOs—would seem, on the face of it, to seek rewards for fields like yours, especially with diabetes and obesity on the rise. But that does not appear to be the case. Why is there a disconnect?**

Grunberger: First, who thought you could put more people into the system and decrease costs? If you promise to insure more people, increase their access to medical care, and increase the quality of care, then it's going to cost more. It's going to be impossible to meet all 3 goals – the premise is just impossible.

Second, how do you make any forecasts in the management of a chronic disease? When a patient has obesity, hypertension, dyslipidemia, and/or diabetes, managing the diseases is a lifelong commitment.

I know how to fix it: Focus on prevention rather on than spending trillions of dollars on people who are already seriously ill. However, no one in politics seems to be interested in doing that.

Healthcare, by definition, should be focused on maintaining the health of people. If you focus on screening and prevention so people don't get sick in the first place, it costs less to serve more people. We haven't done that, and we are now stuck in an epidemic of these metabolic diseases.

EBDM: **One of the changes endocrinologists have experienced is the policy change by the Centers for Medicare & Medicaid Services (CMS), which on January 1, 2010, replaced the consultative codes that your field used with other billing codes. How has this affected your practice, and what does it mean for the ongoing shortage in the field?**

Grunberger: My reimbursements both by Medicare and private insurers have been cut. I've been in the field for well over 30 years, but think about someone who is looking at what I am looking at. Think about how the system is structured: Medical students incur $250,000 in debt, so why would they pursue additional lengthy training in a cognitive specialty when they cannot make a living in it? It's going to be quite challenging. There are already more pediatric endocrinologists dying and retiring each year than are being trained.

We also have to think about the standard of care. Evaluating a new patient cannot be done well in 30 minutes. With 26+ million people with diabetes today, if each one needs to see their doctor a minimum of 4 times a year, that's 100 million visits if all goes well. And there's so many additional things we need to do during that encounter. There are many more medications to consider and discuss; with our increased knowledge, discussions and documentations have become more complicated.

Consider that the better diabetes specialist I am, the less time I have to spend with each person to make a decision on next steps in their care, and the fewer times they have to see me. But right now, there's no incentive for me to do that since I would make less money and not be able to stay in business to provide that care.

A good endocrinologist can supervise a dozen mid-level providers. If someone would allow me to do that, I could have 12 physician assistants, nurse practitioners, and diabetes educators who I would be able to supervise, and I could make the critical decisions in about 30 seconds and move on to the next patient. But right now, I can get paid only if I see the patient for the entire duration of the encounter. This makes no sense—look at how other industries are run. Yet no one in 35 years, no one—not the insurance companies—has ever sought my advice on the ways to leverage the knowledge and experience of an expert to provide better care in an efficient manner.

Economically, it's just becoming impossible. I don't see where the new experienced doctors will come from. We can train more primary care physicians (PCPs) to provide basic endocrinology care, but then who is going to take care of the other patients' medical needs?

EBDM: **What must be done to change the dynamic to get more new doctors to go into endocrinology?**

Grunberger: It's very simple: given the speed and complexity in which new knowledge is acquired we will have more and more people who need specialists to provide their care. Given the mass of people who are going to need us given the twin epidemics of obesity and diabetes in addition to all the other endocrine issues (osteoporosis, thyroid,

dyslipidemia, etc, etc), we need more endocrinologists who are actively providing clinical care. Many excellent endocrinologists got so discouraged they have left for academia, the pharmaceutical industry, insurance companies, FDA, and other places in which they do not provide full-time endocrine care. We have to make it more attractive for them to work directly with patients again. More physicians need to choose cognitive specialties like endocrinology, rheumatology, or infectious disease, but these require an additional 2 to 3 years of training. We must try incentives like loan forgiveness, or other financial means. People follow the dollar signs.

EBDM: **What are the long-term implications of the way the system fails to reward endocrinologists?**

Grunberger: I am so much less expensive than an invasive cardiologist. Yet the way we make decisions in healthcare does not put value on what it takes to become a great endocrinologist. People don't understand how much time, training, and investment goes into making a doctor a true expert. Until someone gets sick, the quality of a doctor is not a priority.

Endocrinology is an intellectual subspecialty; you have to think and then transmit the outcome of the thinking process to a patient in a comprehensible manner rather than just perform a procedure on a passive patient. To pass the knowledge from one generation to the next, there has to be a pipeline of eager, intellectually curious, and ambitious young physicians. In addition, we have to provide financial incentives for endocrinologists who have left clinical practice to come back. The basic science discoveries are moving fast, and the potential translation into clinical practice is getting wider, so much so that I worry: who is going to train the new generation of outstanding clinical endocrinologists? It's not just a question of who will pick this specialty, but how will we make sure their teachers are still around? **EBDM**

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ADA Conference Coverage 2013

Abrahamson: For T2DM, Sulfonylureas Still Useful Second-Line Therapy With Metformin

Mary K. Caffrey

It's too soon to write an epitaph for sulfonylureas as a second-line therapy with metformin, given the large number of patients with type 2 diabetes mellitus (T2DM) who can benefit from them, according to Martin J. Abrahamson, MD, FACP, medical director at the Joslin Clinic and associate professor of medicine, Harvard Medical School.

The arrival of incretins, coupled with a 2012 report that sulfonylureas caused more cardiac issues than metformin in a large study of veterans,[1] has generated debate over the future of sulfonylureas, which lower blood glucose by increasing the secretion of insulin from pancreatic β-cells.[2]

In his presentation at the 73rd Scientific Sessions of the American Diabetes Association in Chicago (June 21-25), Abrahamson said there is consensus that metformin is the first-line therapy of choice. But for those patients who cannot achieve therapeutic goals quickly—and Abrahamson said it is key that they do so—sulfonylureas should remain a second-line option for many patients, except those who are at risk for hypoglycemia. It is especially urgent, he said, to bring blood sugar (A1C) levels below 7%.

Diabetes is a progressive disease, and studies show that the closer the newly diagnosed patient is to therapeutic goals for A1C, blood pressure, and low-density lipoprotein (LDL), the easier it will be for the patient to reach those goals.[3]

Thus, when a single agent does not work, Abrahamson said, "Combination therapy is going to be needed early on if the patients are going to achieve therapeutic goals." And while there is agreement that metformin should be tried first, "There is no consensus on what to add next."

Martin J. Abrahamson, MD, FACP

Abrahamson reviewed recent studies to evaluate sulfonylureas and alternatives alongside metformin based on their effectiveness, tolerability, cardiovascular effects, durability, and cost. He compared sulfonylureas with thiazolidinediones (TZDs), dipeptidyl peptidase inhibitors (DDP-IVs), glucagon-like peptide receptor (GLP-1) agonists, and insulin. He excluded sodium glucose co-transporter 2 inhibitors because they were too new to the market. (The US Food and Drug Administration granted approval on March 29, 2013.[4])

While acknowledging the debate, Abrahamson said that for now it makes no sense to abandon sulfonylureas as a second-line therapy, given how they compare with alternatives, using today's yardsticks. As long as factors like effectiveness, side effects, and cost are what doctors have to go by, they are the criteria that must be used. "Unfortunately, these are the parameters that we have to focus on, because phenotypic and genotypic approaches to determine the most effective therapy are still lacking," Abrahamson said. A decade from now, that may not be true, he said.

Among the concerns about sulfonylureas is the suspicion that long-term use contributes to a decline of β-cell function, or "burnout." A study published in November 2012 in *Diabetes Technology & Therapeutics* found an association between extended sulfonylurea use and deteriorating β-cell function, but not a causal link.[5] In his review, Abrahamson noted this lack of proof, saying of sulfonylureas, "There is no clear evidence that they hasten the demise of the β-cell."

Two key advantages of sulfonylureas, based on Abrahamson's presentation, are their low cost and the limited need for monitoring, compared with alternatives. With the economic cost of diabetes reaching $245 billion a year in the United States,[6] including $18 billion for glucose-lowering medications, price is necessarily a consideration for both doctor and patient, Abrahamson said. Some 26 million Americans have diabetes,[6] and 80% are treated by their primary care physicians, Abrahamson said, making simplicity of monitoring essential.

Notably, he said, in many cases "submaximal" doses of sulfonylureas have been shown to be as effective as maximal doses.[7]

Still, Abrahamson said, "We need more data," and "It's coming." In June, the National Institutes of Health launched GRADE (Glycemia Reduction Approaches in Diabetes), a comparative effectiveness study that will randomize 5000 patients

taking metformin and 1 of the following: sitagliptan (Januvia), a DPP-IV inhibitor; glimepiride (Amaryl), a long-acting sulfonylurea; liraglutide (Victoza), a GLP-1 agonist; and glargine (Lantus), a long-acting insulin analogue.[8]

For now, he cautioned, "Which sulfonylurea you choose, and what dose you use does matter." **EBDM**

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Restorative Yoga Better Than Stretching for Trimming Subcutaneous Fat in Overweight Women

Mary K. Caffrey

Almost any doctor would tell an overweight patient—especially one who gets little activity—to start exercising. But for the obese, those with a body mass index (BMI) of 30 kg/m^2 or higher, just getting started can be daunting.

With that in mind, Maria G. Araneta, PhD, MPH, of the University of California, San Diego, designed a study to determine whether obese women would see a loss of fat from less intense exercise than aerobic activity, which is known to increase the heart rate and burn calories and fat. She presented results gathered with co-authors Matthew A. Allison, MD, MPH, Elizabeth Barrett-Connor, MD, and Alka M. Kanaya, MD, at the 73rd Scientific Sessions of the American Diabetes Association in Chicago (June 21-25).[1]

Smaller studies had shown other health benefits from yoga to persons at risk of diabetes,[2] but Araneta said no study had specifically measured a loss of fat. Araneta and her colleagues wanted to know who would benefit more: women who took part in a 48-week program of restorative yoga, or those who engaged in a program of stretching exercises. Their findings showed that the restorative yoga practitioners lost significantly more subcutaneous fat over the initial 6 months of the study period, and kept losing it during a maintenance period with less direct supervision. There was no significant loss of visceral fat in either group.

The difference between restorative yoga and other forms is key: Unlike more intense forms of the ancient practice, restorative yoga does not feature flowing body movements or challenging balance poses. As Araneta said, "The postures focus on relaxation and stress reduction and are more feasible for overweight individuals."

While stretching and body alignment are involved, restorative poses are often performed in a reclined or seated position, with limbs and parts of the torso supported by blankets, pillows, or padded bolsters that resemble a sofa cushion. Poses are held much longer than in other styles of yoga, often as long as 7 minutes. Measured breathing is emphasized, and many commercial classes feature meditative music.

Photo Credit: RAVI BHATIA PHOTO/SessionsWithRAVI@gmail.com

The yoga group (n = 88) had a mean age of 55 years, and an average BMI of 36 kg/m^2. The stretch group (n = 83) had a mean age of 54 years, and an average BMI of 32.5 kg/m^2. Despite this difference, Araneta said, there were not significant differences in weight and subcutaneous fat between the 2 groups at the start of the study. All participants had metabolic syndrome as defined by International Diabetes Foundation (IDF) criteria.

Study subjects received medical evaluations at 3-month intervals, with subcutaneous and visceral fat being measured between the L4 and L5 vertebrae with a 16-detector helical computer topography (CT) abdominal scanner.

Participants received semi-weekly and then weekly classes in the first 12 weeks, then bi-weekly classes to the 6-month mark. The final weeks served as a "maintenance period," when participants were asked to do their yoga poses or stretching exercises largely on their own, with classes only once a month.

Both groups lost weight, with the restorative yoga practitioners losing more, an average of 1.3 kg at 6 months compared with 0.7 kg for the stretch group. Significantly, the yoga group maintained the reduction, with the average weight loss reaching 1.7 kg at the 48-week mark, even when controlling for BMI.

The difference in subcutaneous fat loss between the groups was more pronounced, however. The restorative yoga group lost 31 square centimeters at 6 months, compared with 12 square centimeters for the stretch group. At 48 weeks, the yoga group had continued its loss to 34 square centimeters, while the stretch group was moving in the other direction, back to 6.6 square centimeters.

One explanation for the difference may be that restorative yoga reduces levels of cortisol, which rises during times of stress and is known to increase abdominal fat. Contacted in August, Araneta said her team is reviewing data on cortisol, and results will be released later in 2013.

In Chicago, Araneta did not present restorative yoga as a replacement for aerobic activity; rather, she said this "complementary, ancient practice" could serve as a means of gentle movement for those severely obese patients for whom other activity is not practical.

The study was funded by the National Institutes of Health.

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Does Sugar Cause Cardiometabolic Disease? Stanhope Reviews the Evidence

Mary K. Caffrey

Consuming too much sugar makes us gain weight, and being overweight is associated with poor cardiovascular health. But while multiple epidemiological studies have found an *association* between sugar intake and cardiometabolic disease, tagging sugar as the *cause* is another matter, according to Kimber Stanhope, PhD, RD, a nutritional biologist at the University of California-Davis.

Moving sugar, or at least some forms of it, from being linked to heart disease to being an actual cause is no small matter, Stanhope explained. Such a change, she said, requires "direct experimental evidence." Her group and others have studied sugar intensely in recent years, as the epidemics of obesity and diabetes have soared in the United States.[1]

Stanhope's presentation at the 73rd Scientific Sessions of the American Diabetes Association in Chicago (June 21-25), "Does Sugar Consumption Contribute the Epidemics of Metabolic Disease?",[2] offered a review of her own ground-breaking work[3] and that of others, notably the 2012 Maersk study,[4] which found increases in liver fat among overweight patients who consumed drinks containing sucrose, compared with those drinking low-fat milk, water, or drinks with aspartame.

In 2012, news media—including Sanjay Gupta, MD, on *60 Minutes*—began to attach the label "toxin"[5] to sugar, based on Stanhope's 2011 article in the *Journal of Clinical Endocrinology & Metabolism,* which found adverse cardiometabolic effects on healthy, young patients after only 2 weeks of drinking beverages with high-fructose corn syrup.[3] She shared additional unpublished data from this ongoing study, which so far confirm the initial findings. (Earlier studies by Stanhope's team had involved older patients who were already overweight.)

Kimber Stanhope PhD, left, discussed the cardiometabolic effects of sugar on young adults with Sanjay Gupta MD on 60 MINUTES on April 1, 2012.

Stanhope's studies are highly involved. Participants must live at the research center for all or part of the time; while inpatient, they consume only those foods served by the study team. Every calorie is recorded, and frequent tests measure triglycerides, blood pressure, cholesterol, and uric acid, both after meals and after fasting. As she explained, the requirements of achieving the "gold standard" in nutritional research is one reason why moving from associating sugar with heart disease to showing a causal link is so difficult.

Much of Stanhope's presentation focused on her findings on the differences between fructose and glucose, which has been the subject of critical papers published in 2009 and 2011.[3,6] Stanhope took her audience on a tour through how each sugar travels through the liver, showing the key differences between how glucose and fructose are processed—and why the processed fructose in modern beverages stays put in the liver while glucose does not. This is true, she said, even when weight gain among test groups is the same.

As her presentation highlighted, Stanhope's current study design of young adults does not occur in a vacuum. She noted the large discrepancy between the 2009 recommendation by the American Heart Association (AHA), which called for women to limit their added sugar to 100 kilocalories (kcal) per day, with men limiting theirs to 150 kcal/day, and that of the August 2010 Dietary Guidelines for Americans. The official effort undertaken every 5 years by the US departments of Agriculture and Health and Human Services, the Dietary Guidelines issued conflicting advice. As Stanhope noted, the Dietary Guidelines called for no more than 25% of energy to come from added sugar.

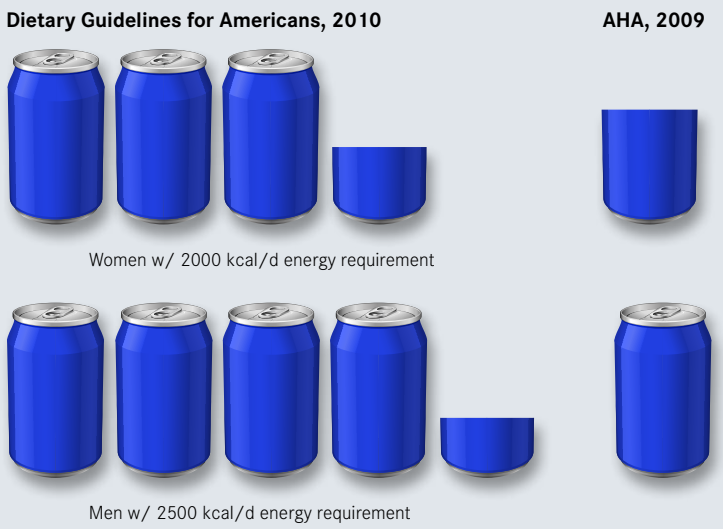
Stanhope illustrated the gap with a slide of soda cans, which looked suspiciously like Coca-Cola. For men, the difference was between 4 1/3 cans for the Dietary Guidelines recommendation and a single can for the AHA's.

"Clearly, in 2010 there was controversy in the role of sugar in the epidemics of metabolic disease," she said. What about today? The question remains unsettled, Stanhope said, but the abundance of epidemiological evidence, combined with very recent direct experimental evidence, suggests that sugar *could* be a cause of heart disease.

The real question, Stanhope said, is whether it makes sense to wait for sugar to be deemed the culprit conclusively before we act. "Do we need to wait for these results before we revise the Dietary Guidelines for Americans and start educating the public accordingly?" she asked.

Her comments were timely. Just a week earlier, the new advisory panel that will shape the 2015 Dietary Guidelines for Americans had held its first meeting in Bethesda, Maryland.[7] The group is scheduled to take testimony October 3-4. **EBDM**

Table 1. How Much Sugar Should Adults Consume?



Adapted from chart presented by K Stanhope at ADA (June 21-25, 2013), Chicago, Illinois. Comparison of 2010 recommended percentage of energy kilocalories as added sugar, Dietary Guidelines for Americans, with 2009 recommendations for added sugar, American Heart Association.

Photo Credit: CBS NEWS PHOTO

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THE AMERICAN JOURNAL OF MANAGED CARE

Limiting Students' Diabetes Management to School Nurses Does Not Improve Parents' Perception of Safety, Study Finds

Mary K. Caffrey

Dealing with a child's diabetes during the school day can be challenging for all involved, so much so that in some studies parents have described it as "the worst experience,"[1] Kimberly A. Driscoll, PhD, an assistant professor at Florida State University, told an audience at the 73rd Scientific Sessions of the American Diabetes Association (ADA) meeting in Chicago (June 21-25, 2013).

It's little wonder, then, that states are split on who should be charged with blood glucose monitoring or handling a student's diabetic episode during school hours. Despite longstanding recommendations and an ADA campaign calling for adults beyond the school nurse to be trained to assist with monitoring or administer insulin or glucagon,[2] Driscoll's map of states showed about half limit such tasks to school nurses, other licensed medical personnel, or the child's parent.[3]

Do these restrictions make students safe? Driscoll asked that question in her study, and presented the first round of results in Chicago. Parents of 464 children with type 1 diabetes mellitus (T1DM) were surveyed at major diabetes centers in Texas, Colorado, Massachusetts, and Pennsylvania. Driscoll selected 2 states—Texas and Colorado—with laws based on ADA guidelines calling for personnel other than school nurses to be trained to administer insulin and glucagon, and 2 other states—Massachusetts and Pennsylvania—where state law limit these tasks to the school nurse.

In the study, Driscoll controlled for students' race, their blood sugar level (A1C), and how long they had lived with T1DM. For most purposes, Texas and Colorado students were treated as one group, and Massachusetts and Pennsylvania students were treated as another group. The ADA funded the study.

Driscoll's work expanded on a 2005 survey by Hellems and Clarke[4] of Virginia parents, who were studied 6 years after that state became the first to allow non-nursing personnel to treat children with diabetes at school. (They were given immunity from liability.) Parents were asked who took care of their child, and Driscoll noted, "One thing that was striking was the number of parents who said that no one was helping their children."

But the Hellems and Clarke study did not examine parents' perceptions of their children's safety, which Driscoll aimed to do.

What the Survey Found

Driscoll's survey expanded the 2005 questionnaire. Parents were asked to recall how many incidents of low blood sugar and high blood sugar—with symptoms—their children had experienced at school within the past 3 months. The study's authors aimed to ensure that parents had strong memories of recent incidents involving their children's diabetes, Driscoll said.

In both groups, just above 50% of the children had between 1 and 5 low A1C events in the prior 3 months, with "low" defined as <70% mg/dL. The number of incidents of high A1C, with "high" defined as >250mg/dL, was more evenly distributed among children experiencing up to 5, from 6-10, 11-15, or >15 incidents. Of note, in both the low and high A1C results, distribution was consistent between the Texas/Colorado group and the Massachusetts/Pennsylvania group.

In both groups, parents reported that their children most frequently administered their own insulin during low A1C episodes, while the school nurse most frequently administered it when the child experienced high A1C.

According to Driscoll's results, incorrect doses are relatively infrequent, but they do occur: Out of 464 parents taking the survey, 22 in the Texas/Colorado group reported an incorrect dose in the previous 3 months, while 8 in the Massachusetts/Pennsylvania group reported a wrong dose in that period. In both groups, the most frequently cited person administering the wrong dose was the school nurse, followed by the child with diabetes.

Kimberly A. Driscoll, PhD

Thus, Driscoll said, even though there were more incidents in the states that allow non-nursing personnel to treat children, "In all our states, the parents perceived it was the school nurse, who are the experts, making the mistakes."

Do Parents Feel Safe?

Driscoll's questions on whether parents feel safe—and how safe they feel—distinguished this study from earlier parent surveys. On balance, most parents in all 4 states felt safe (40% Texas to 60% for Massachusetts) or very safe (2% Pennsylvania to 40% for Texas); she reported that there was no statistical difference between the states that limited treatment to the school nurse, compared with those that allowed other personnel to administer insulin or assist with blood glucose monitoring.

Also, despite some minor fluctuations, Driscoll said there was also no statistical difference between parents' perceptions of safety during the school day and at after-school activities, such as clubs, sports, or school trips. (In response to questions, however, sports coaches ranked high among those parents hoped would receive training in diabetes care.)

Still, Driscoll reported there were significant subsets in the 4 states (8% Massachusetts to 18% for Colorado) who reported feeling that their children are unsafe. Perhaps more alarming, she said, is the small share (2% Massachusetts to 15% for Pennsylvania) who report they "don't know" or did not answer whether their child is safe at school.

"Overall, most of the parents are very satisfied," Driscoll said. "Parents in states that allowed trained personnel to administer insulin reported they perceive similar safety and satisfaction. Even though there were a small percentage who were not satisfied, parents were equally satisfied with diabetes care, regardless who provides the care."

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versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

Hypoglycemia: In all clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14) in full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 4) *[see Warnings and Precautions]*.

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0
In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Laboratory Tests: *Increases in Serum Potassium:* Dose-related, transient mean increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 3 weeks) in a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*. In this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. More severe elevations (i.e., equal or greater than 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. In patients with moderate renal impairment, increases in potassium were more commonly seen in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions]*.

Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was 8.1% and 9.3% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Serum Phosphate: Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo controlled trials, the mean change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Warnings and Precautions]*.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

DRUG INTERACTIONS

UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Digoxin: There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA in nine clinical studies of INVOKANA *[see Clinical Studies (14.3) in full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA1C with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2); patients treated with INVOKANA 300 mg were more likely to experience increases in potassium *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Adverse Reactions]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

OVERDOSAGE

There were no reports of overdose during the clinical development program of INVOKANA (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Instructions: Instruct patients to read the Medication Guide before starting INVOKANA (canagliflozin) therapy and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

Inform female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.

Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions such as urticaria and rash have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema, and to take no more drug until they have consulted prescribing physicians.

Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

Active ingredient made in Belgium

Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from Mitsubishi Tanabe Pharma Corporation

10282400

K02CAN13080B

janssen

THE AMERICAN JOURNAL OF MANAGED CARE

The Clinical and Economic Consequences of Obesity

Caroline M. Apovian, MD

Obesity as a category is defined as the possession of a body mass index (BMI) of 30 or more, whereas "overweight" is the term used to describe an individual with a BMI greater than or equal to 25 but less than 30.1 The prevalence of obesity among adults in the United States, according to a CDC study using data from the National Health and Nutrition Examination Survey, was 35.7% during 2009 to 2010, amounting to more than 78 million people over the age of 20 years.[2] More than two-thirds of US adults (68.5%) aged 20 to 74 years had a BMI of at least 25 during 2007 to 2010.[3] Worldwide, it is estimated that nearly half a billion adults are obese, while overweight and obesity constitute the fifth-most common cause of death globally.[1] The situation is worsening each year. A recently published forecast for obesity estimated that over the next 20 years, the prevalence of obesity in the United States will increase by 33%, and that the prevalence of a BMI of 40 or higher will increase by 130%.[4] In this article, we will review the clinical and economic consequences of obesity and related comorbidities, including impact on quality of life (QoL); discuss the cost-effectiveness of interventions to treat obesity; and examine the impact of weight loss on health outcomes, costs, and QoL.

Table 1. Prevalence of and Total Number of Persons With Diabetes, Hypertension, and Dyslipidemia in the General Population of the United States[8-11,a]

Condition	Year(s)	Prevalence	Total Number of Persons
Diabetes	2010	8.3% (all ages)	25.8 million
Hypertension	2005-2008	30.9% (aged 18 y and over)	68 million
Elevated LDL cholesterol	2005-2008	33.5% (aged 20 y and over)	71 million
Elevated triglycerides	2007-2010	27% (aged 20 y and over)	(not available)

LDL indicates low-density lipoprotein.
[a]Overlap between populations is possible.

Obesity-Related Comorbidities

The consequences of obesity can be understood, in part, by examining the many comorbidities with which obesity is linked, an understanding of which necessarily precedes a discussion of the clinical and economic consequences of obesity. Obesity is associated with numerous cardiovascular risk factors, including diabetes, hypertension, and dyslipidemia.[5,6] Types of dyslipidemia include elevated low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein (HDL) cholesterol, and elevated triglycerides.[7] **Table 1** shows the overall prevalence in the general US population of diabetes, hypertension, and elevated LDL cholesterol, along with the total number of persons with these conditions.[8-11] In addition to being associated with several cardiovascular risk factors, obesity is associated with an increased risk of all-cause mortality.[12]

Field et al provided a sense of the scale of the relationship between excess weight and comorbid diseases by determining the effect of having a BMI over 25 on the risk of experiencing 7 different obesity-associated comorbidities during a 10-year period of follow-up (1986-1996). Data for this study were derived from 77,690 women participating in the Nurses' Health Study and 46,060 men participating in the Health Professionals Follow-Up Study, offering robust data from 2 large-scale studies.[5] **Table 2** shows the adjusted odds ratios for men and women with a BMI of 30.0 to 34.9 and those with a BMI of 35.0 or greater experiencing these 7 comorbidities compared with men and women with a BMI between 18.5 and 24.9. The elevation in diabetes risk is most notable, with obese women having a 10- to 17-fold increased risk of the disease, and obese men having an 11- to 23-fold increased risk. Hypertension and gallstones were also seen at significantly higher rates in obese men and women, while heart disease was 2 to 2.2 times more likely in obese men.[5]

These data are consistent with the results of a meta-analysis by Guh et al of studies examining the relationship between obesity and selected comorbidities, which found that obesity was associated with increased risk for a variety of diseases and disease risk factors. The relative risk (RR) for congestive heart failure in obese subjects was 1.79 for men and 1.78 for women, while the RR for stroke was 1.51 among obese men and 1.49 among obese women. Risk of pulmonary embolism was notably high, with an RR of 3.51 for both men and women. Like the study by Field et al, the meta-analysis by Guh et al found that obesity was strongly associated with the incidence of type 2 diabetes mellitus, with obese men having an RR for diabetes of 6.74 and women an RR of 12.41. The meta-analysis also observed an increased risk of several types of cancer among obese patients, including colorectal, endometrial, renal, ovarian, and pancreatic cancers.[13]

Results from a German study of 7124 adults representing a nationally representative sample (the German National Health Interview and Examination Survey) similarly found significantly increased risks among obese compared with non-obese subjects for cardiovascular diseases, cardiometabolic risk factors, osteoarthritis, and, among women, diabetes and gallbladder disease.[14]

The association between obesity and stroke risk was the subject of a 2010 systematic literature review, which comprised 25 studies and over 2 million subjects. The results of the review showed that among obese subjects the RR for ischemic stroke was 1.64 (95% confidence interval [CI], 1.36-1.99; P <.0001), and the RR for hemorrhagic stroke was 1.24 (95% CI, 0.99-1.54; P = .059).[15]

The link between obesity and osteoarthritis—in addition to data previously cited—was well-illustrated in a British cohort study evaluating risk of knee osteoarthritis in 3035 men and women who had been followed from the time of their birth, in 1946, as part of a larger long-term health study. A

Table 2. Ten-Year Risk of Developing an Obesity-Related Comorbidity Among 77,690 Women in the Nurses' Health Study and 46,060 Men in the Health Professionals Follow-up Study[5]

	Adjusted Odds Ratios (95% CI)[a]						
	Diabetes	Gallstones	Hypertension	High Cholesterol Level	Colon Cancer	Heart Disease	Stroke
Women							
BMI between 30.0 and 34.9	10.0 (8.4-11.8)	2.5 (2.3-2.7)	2.1 (1.9-2.2)	0.9 (0.9-1.0)	1.3 (1.0-1.7)	1.5 (1.3-1.7)	1.0 (0.8-1.4)
BMI >35.0	17.0 (14.2-20.5)	3.0 (2.7-3.3)	2.3 (2.1-2.6)	0.7 (0.6-0.7)	1.8 (1.3-2.6)	1.5 (1.3-1.8)	1.1 (0.8-1.7)
Men							
BMI between 30.0 and 34.9	11.2 (9.3-13.6)	2.3 (1.9-2.7)	2.7 (2.4-3.0)	1.2 (1.1-1.3)	1.7 (1.2-2.4)	2.0 (1.7-2.3)	2.0 (1.5-2.7)
BMI >35.0	23.4 (19.4-33.2)	2.9 (2.1-4.1)	3.0 (2.3-3.9)	1.3 (1.1-1.6)	1.3 (0.5-3.2)	2.2 (1.5-3.1)	2.3 (1.2-4.4)

BMI indicates body mass index; CI, confidence interval.
[a]Adjusted for age, smoking status, and race.
Adapted from Field AE, Coakley EH, Must A, et al. *Arch Intern Med.* 2001;161(13):1581-1586.

strong association between BMI and knee osteoarthritis was observed, and the association between BMI earlier in life and knee osteoarthritis later in life could be detected in men as early as age 20 years, continuing uninterrupted to age 53 years, while for women, the effects of BMI were observed as early as age 15 years and going forward.[16]

Excess weight is also associated with nonalcoholic fatty liver disease (NAFLD), a chronic disease that may progress to end-stage liver disease.[17] An analysis of data from the National Health and Nutrition Examination Study from 1988 to 1994 showed that NAFLD was more common in overweight and obese individuals compared with normal-weight individuals.[18] Based on the same analysis, NAFLD was estimated to affect 19% of the US population (95% CI, 17.5-20.6).[18]

With regard to the relationship between sleep and obesity, in adults, sleep deprivation has been associated with risk for overweight and obesity, with an association generally being made between a lack of sufficient sleep and a consequent increase in caloric intake (mainly from between-meal snacking) that promotes weight gain.[19,20]

Obesity is also a strong risk factor for sleep apnea, as evidenced by study data showing associations between newly diagnosed sleep apnea and recent weight gain, as well as data showing increasing sleep apnea severity over time in patients with increasing BMI.[21,22] Obese patients who have Obesity Hypoventilation Syndrome (OHS), also known as Pickwickian Syndrome—a condition characterized by obesity, daytime hypoventilation, and sleep-disordered breathing or sleep apnea—experience even greater health risk, and OHS patients have generally higher mortality rates than similarly obese individuals with sleep apnea alone.[23,24]

In addition to its substantial effects on physical comorbidities, obesity has been shown to exert a deleterious effect on psychological health. Results from a meta-analysis by Luppino et al showed that persons with a BMI of 30 or greater at baseline had a 55% (95% CI, 22%-98%; P <.001) greater risk of developing depression during the follow-up period compared with persons with a BMI between 18.5 and 24.9.[25]

As discussed in this section, excess body weight is associated with negative effects in terms of physical comorbidities and psychological health. In particular, obesity is associated with increased risk of type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular diseases, osteoarthritis, sleep apnea, and several cancers.[5,13,14,21,22,26]

Economic Burden of Obesity

Estimating the cost of obesity is challenging because obesity is related to numerous other comorbidities, many of which are associated with high medical expenditures. For example, in 2010, based on Medical Expenditure Panel Surveys (MEPS) data, the total cost of treatment for patients with diabetes mellitus was $51.3 billion, 48% of which was due to medication costs; the total cost of treatment for patients with hypertension was $42.9 billion, 47.4% of which was due to medication costs; and the total cost of treatment for patients with hyperlipidemia was $37.2 billion, 69.1% of which was due to medication costs.[27]

Capturing the full economic impact of obesity is a complex task. One approach to the study of obesity-related expenditures, conducted by Finkelstein et al, applied data from the 2006 MEPS and the National Health Expenditures Accounts to identify total annual medical costs.[28] The authors compared expected costs among people of normal weight with the costs observed in obese subjects to arrive at a relative increase in per capita spending related to obesity. They found that in 2006, medical expenditures in obese patients were 41.5% higher than expenditures in patients of normal weight, amounting to an annual per capita difference of $1429 (in 2008 dollars). When broken down by type of insurer, the annual costs associated with obesity were 58.1% higher ($1140) for those who were privately insured, 36.4% higher ($1723) for Medicare patients, and 46.7% higher ($1021) for Medicaid patients. The authors further broke down that expenditure data by type of insurer and type of service. Among those covered by private insurance, the annual inpatient costs were 90.3% higher ($443) for obese patients, the non-inpatient costs were 37.9% higher ($398), and the prescription drug costs were 81.8% higher ($284), compared with normal-weight individuals. The relative difference for inpatient expenditures among private insurers was far higher than differences seen in Medicare and Medicaid inpatient costs. By contrast, although prescription drug and non-inpatient costs were higher in obese patients for all insurer types, these differences were less marked between private insurers, Medicare, and Medicaid (**Table 3**).[28]

MEPS data were also used by Cawley et al, who estimated the total US annual expenditures attributed to obesity-related illness to be as high as $209.7 billion annually (in 2008 dollars), which is equivalent to 20.6% of US health expenditures. The medical costs of obesity-related illness impacted all healthcare sectors and payers.[29]

Table 3. Additional Per Capita Spending in Obese Adults in 2006 by Insurance Category and Service Type (2008 dollars)[28]

Insurance Category	Type of Service	Spending Increase ($)	Percent Increase
Medicare	Inpatient	95[b] (296)	4.4[b] (13.0)[a]
	Non-inpatient	693[c] (128)	40.1[c] (8.4)
	Prescription drug	608[c] (65)	72.7[c] (10.3)
Medicaid	Inpatient	213[b] (153)	39.2[b] (34.2)
	Non-inpatient	175[b] (172)	14.8[b] (12.8)
	Prescription drug	230[b,c] (80)	60.6[b,c] (24.2)
Private	Inpatient	443[c] (85)	90.3[c] (23.9)
	Non-inpatient	398[c] (60)	37.9[c] (6.6)
	Prescription drug	284[c] (41)	81.8[c] (12.4)
All payers	Inpatient	420[c] (93)	45.5[c] (12.0)
	Non-inpatient	444[c] (76)	26.9[c] (4.7)
	Prescription drug	568[c] (59)	80.4[c] (8.3)

[a]Bootstrapped standard errors are shown in parentheses.
[b]Relative standard error is greater than 0.3, indicating that the estimate is unstable.
[c]Increased spending estimate is significantly greater than zero (P <.05).

Wang et al evaluated the increase in healthcare costs per unit increase in BMI by analyzing medical and pharmaceutical claims data from 35,932 employees and spouses from various manufacturing companies. Based on their analysis, annual medical costs increased $119.7 (4%) and pharmaceutical costs increased $82.6 (7%) per BMI unit within the BMI range of 25 to 45 (adjusted for age and gender; in 2004 US dollars). Medical costs related to heart disease and diabetes increased by $20.3 and $6.2, respectively, per BMI unit (adjusted for age and gender).[30]

The impact of obesity on medical costs was further seen in a study by Thompson et al, which showed higher rates of pharmaceutical expenditures incurred by obese versus non-obese subjects belonging to the Kaiser Permanente Northwest Division health maintenance organization. Members with a BMI of 30 or greater were found to have 84% more pharmaceutical dispenses than non-obese patients, and overall pharmacy costs that were 105% higher. With regard to diabetes medications alone, obese members had 6 times as many dispenses and incurred costs more than 13-fold greater than non-obese subjects.[31]

As described in this section, obesity exacts a heavy economic burden, with total US annual expenditures attributed to obesity-related illness estimated to be as high as $209.7 billion annually (in 2008 dollars), which is equivalent to 20.6% of US health expenditures. The medical costs of obesity-related illness impact all healthcare sectors and payers.[29] These costs are mainly due to the treatment of obesity-related diseases, rather than the treatment of obesity itself.[28]

Impact of Obesity on Employers

The effect of obesity on employer-incurred healthcare costs as well as lost productivity is substantial and has been the subject of several different analyses. Finkelstein et al looked at the impact of obesity on full-time employees and their employers, drawing data from 2 public data sets: the US National Health and Wellness Survey for 2008, and MEPS for 2006. The data sets included subjects 18 to 64 years old stratified by obesity grades (grade I = BMI 30-34.9; grade II = BMI 35-39.9; grade III = BMI 40+).[32] Medical expenditures, absenteeism, and presenteeism (ie, reduced productivity among workers on-site) were calculated. Total annual expenditures attributable to obesity, including both medical costs and lost productivity, for obese males ranged from $1143 for grade I obesity to $6087 for grade III. Among women, grade I obesity was associated with total annual costs of $2524, while grade III obesity total annual costs were estimated at $6694. Subjects with a BMI of 35 or higher (37% of all subjects in the study) accounted for 61% of excess costs. The Finkelstein study also showed that presenteeism represented the largest contributor to obesity-related cost for employers.[32]

Durden et al studied costs related to overweight, obesity, and BMI of 35 or

higher incurred by self-insured employers using health claims data, self-reported health risk assessment data from employees, and productivity data from 2003 to 2005. Regression models were used to estimate incremental direct and indirect costs in a study population that included nearly 89,000 employees. Direct medical costs associated with overweight, obesity, and BMI of 35 or higher were found, during the study period, to be $147, $712, and $1977, respectively, while indirect medical costs (due to paid absence) associated with overweight, obesity, and BMI of 35 or higher were $1404, $1511, and $1414, respectively.[33]

Finally, Cawley et al sought to determine the nationwide scope of absenteeism cost related to obesity using data from the MEPS for 2000 to 2004. The authors estimated the total annual cost due to obesity-related absenteeism to be $4.3 billion (in 2004 dollars).[34]

In summary, healthcare spending and rates of absenteeism and presenteeism (with associated impact on workplace productivity) are higher among obese workers compared with normal-weight workers, and costs increase with increasing BMI.[32,33]

"Obesity exacts a heavy economic burden, with total US annual expenditures attributed to obesity-related illness estimated to be as high as $209.7 billion annually (in 2008 dollars).

QoL Burden of Obesity

Individuals who are obese have an elevated risk of experiencing poorer QoL compared with non-obese individuals both as a direct result of being obese and as a consequence of the many comorbidities associated with obesity. The European Male Ageing Study (EMAS), which included 3369 men (aged 40-79 years) drawn from 8 European countries, is perhaps the most comprehensive examination of the effects on QoL in the male population.[35] A total of 814 (25%) of the study subjects were obese and 1629 (49%) were overweight; the study subjects' QoL was assessed using 3 instruments: the Short Form-36 (SF-36), the Beck Depression Inventory, and the EMAS sexual function questionnaire. Obesity was found to be associated with a significant increase in risk of performing poorly in a variety of physical function subdomains, including ability to perform vigorous activity, to climb stairs, or to walk more than 1 km, while also being associated with impairment of 1 or more, 2 or more, or 3 or more physical functions. Several psychological elements were additionally significantly impacted in obese patients, including loss of energy, sleep changes, and various measures of tiredness. Sexual function subdomains were also, in most cases, significantly lower in obese men.[35]

The negative effect of obesity on QoL manifests in patients of all ages. Among older patients, this fact is confirmed not only by the EMAS data but also by a study from the University of California, San Diego, involving 1326 adults with a mean age of 72 years, which showed significantly poorer "Quality of Well Being" scores among obese subjects compared with those who were overweight or who had normal BMI.[36] A Swedish study of younger women, aged 18 to 34 years, meanwhile, found that compared with normal-weight women, obese women in this age group were more likely to be unemployed, less likely to be engaged in academic studies, more likely to possess limited emotional support, more likely to have lower self-reported physical health, and more likely to smoke.[37] The relative severity of impact of obesity on QoL was evaluated in a recently published study of very obese patients awaiting weight loss surgery; the results showed that the QoL of these patients was similar to the QoL of patients living with diabetes or laryngeal cancer.[38]

As discussed in this section, excess body weight is associated with negative effects on QoL, and the negative impact of obesity on QoL affects both male and female patients of all ages.[35-38]

Cost-Effectiveness of Interventions to Treat Obesity

Studies of interventions to treat obesity are fairly consistent in observing cost-effectiveness across a spectrum of different treatment modalities. A systematic literature review and meta-analysis conducted by the UK's Health Technology Assessment program and published by Ara et al examined the clinical effectiveness and cost-effectiveness of pharmaceutical therapies for obesity in primary care, and included 94 studies comprising 24,808 subjects. With regard to efficacy, drug interventions (in addition to lifestyle interventions) were shown to reliably reduce weight and BMI in obese patients in the short term (up to 12 months). In terms of cost-effectiveness, 16 pharmacoeconomic studies were reviewed, comparing 3 drugs (orlistat, sibutramine, and rimonabant) then available in the United Kingdom for obesity treatment; the authors' analysis demonstrated high degrees of cost-effectiveness associated with all of the studied agents.[39] It should be noted that the literature review and manuscript preparation for the Ara et al publication occurred in 2009 to 2011, and thus the meta-analysis does not include pharmaceutical therapies that were more recently approved by the US Food and Drug Administration. These results are consistent with the results of another literature review, which included 14 studies evaluating cost-effectiveness or cost-utility with the same 3 drugs. This review also found these agents to be cost-effective, although the sustainability of weight loss was uncertain.[40]

Sibutramine was the subject of a US study published in 2005, comparing its use versus non-use in a group of 501 patients participating in a weight management program. The authors determined that sibutramine did help subjects achieve significantly greater weight loss and BMI decrease, but that its use was not associated with cost savings. It should be noted, however, that subjects receiving sibutramine were significantly older and had a higher BMI than subjects not receiving sibutramine.[41]

Also recently published was a study evaluating the efficacy and costs of a stepped-care weight loss intervention (STEP) and a standard behavioral weight loss intervention (SBWI) in 363 overweight and obese adults randomized to 1 of the 2 interventions for 18 months.[42] Both interventions resulted in significant weight reductions after 18 months (both P <.001 vs baseline), with reductions in the SBWI group being greater, but not significantly so, than reductions in the STEP group (–8.1% vs –6.9%). Patients in both treatment groups experienced significant reductions in resting heart rate and blood pressure as well as increases in fitness. Although the study did not include a cost-effectiveness analysis, the costs associated with treatment were, in both the STEP group and the SWBI group, notably lower than medical expenditures associated with obesity, with a significant financial advantage for the STEP intervention over the SWBI intervention. Combined payer and participant costs were $1357 (95% CI, $1272-$1442) for the SBWI group versus $785 (95% CI, $739-$830) for the STEP group (P <.001).[42]

Bariatric surgery may be used in patients with a BMI of 40 or greater or patients with a BMI of 35 or greater who have an obesity-related comorbidity (eg, hypertension, hyperlipidemia, obstructive sleep apnea). Additionally, bariatric surgery is FDA approved for use in patients with a BMI between 30 and 35 who have type 2 diabetes mellitus (T2DM). Bariatric surgery has become more common and more diverse in its modalities, comprising techniques such as Roux-en-Y gastric bypass, sleeve gastrectomy, and adjustable gastric banding.[43] The decision to undertake bariatric surgery must involve a balanced view of the medical risks associated with obesity versus the short- and long-term risks of complications related to surgical intervention.[43] In the Swedish Obese Subjects study, for example, 0.25% of subjects died within 90 days of surgery compared with 0.10% of matched controls who did not have surgery. However, cumulative mortality, based on 16-year follow-up, found that 101 patients in the surgery group had died compared with 129 patients in the control group (hazard ratio = 0.76; 95% CI, 0.59-0.99; P = .04).[44]

A systematic review by the Health Technology Assessment program assessed the clinical effectiveness and cost-effectiveness of bariatric surgery in obese subjects and concluded, with some degree of ambivalence, that for people with a BMI of 30 or greater but less than 40, bariatric surgery is, overall, more effective than non-surgical management and, with somewhat less ambivalence, cost-effective in the same patient group.[45] Other studies have tended to confirm the cost-effectiveness of bariatric surgery. Two US studies in managed care organization populations—one from a large-scale managed care database and the other from an independent practice association—both found laparoscopic bariatric surgery to be cost-effective; the former study observed particular cost benefits in patients with diabetes and the latter in women, non-white subjects, and more obese subjects.[46,47]

A recent US study applied a simulated cost-effectiveness model using an average Medicare reference case of a 53-year-old female patient with a BMI of 44. The authors found all 3 of the surgical methods they examined to be

cost-effective, with Roux-en-Y gastric bypass being the most cost-effective, followed by laparoscopic gastric bypass and adjustable gastric banding, the latter 2 methods yielding similar savings.[48]

In summary, a wide variety of interventions—pharmacologic, behavioral/lifestyle, and surgical—offer effective and economically sound options for weight loss in obese patients.

Table 4. Lifetime and 10-Year Gross Per Capita Medicare Savings From Temporary and Permanent Weight Loss Among 1 Cohort Aged 65 to 70 Years[52]

Baseline BMI at Age 65 y	10% Weight Loss With Weight Regain ("temporary")	15% Weight Loss With Weight Regain ("temporary")	10% Permanent Weight Loss	15% Permanent Weight Loss
BMI ≥27 + comorbidity (2.4 million[a])				
Lifetime	$7556	$9933	$9445	$12,912
10 years	$6456	$7831	$8070	$10,180
BMI ≥30 (5.5 million[a])				
Lifetime	$9112	$10,304	$12,392	$14,116
10 years	$7446	$8911	$9053	$12,208
BMI ≥35 (3.3 million[a])				
Lifetime	$7799	$11,109	$13,496	$15,987
10 years	$7654	$8534	$10,126	$13,474

BMI indicates body mass index.
[a]These numbers reflect the number of Medicare beneficiaries within each BMI category, which can be used to determine the available pool of aggregate savings.
Adapted with permission from Thorpe KE, Yang Z, Long KM, Garvey WT. *Health Econ Rev*. 2013;3(1):7.

Impact of Weight Loss on Health Outcomes, Costs, and QoL

To reduce the increased morbidity and mortality associated with obesity, and reduce risk factors for diabetes and cardiovascular disease, the National Heart, Lung, and Blood Institute, in its Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, recommends an initial goal of a 10% reduction in body weight, and maintenance of a lower body weight over the long term.[49] The American Association of Clinical Endocrinologists recently published an algorithm for the management of diabetes which advocates the treatment of the whole spectrum of cardiometabolic disease with an initial and ongoing focus on achieving weight loss to address the underlying pathophysiology of obesity-related diseases. The guidelines advocate lifestyle interventions augmented with obesity pharmacotherapy, as needed, to achieve target weight loss and improvement in comorbidities and disease biomarkers for hypertension, prediabetes and diabetes, and dyslipidemia (ie, blood pressure, glycemic measures, and lipid changes).[50]

Oster et al estimated the lifetime health and economic benefits of sustained modest weight loss (defined as a 10% reduction in body weight) in persons who are obese, using a model that takes into consideration the connection of BMI to the risks and associated costs of hypertension, hypercholesterolemia, T2DM, coronary heart disease, and stroke. These diseases were selected because they, along with their associated complications, account for a majority of total obesity-attributable medical care costs.[51] Based on their model, with a range of results contingent on baseline variables, the authors showed that sustained modest weight loss would reduce the number of patient years of life with hypertension by 1.2 to 2.9 years, hypercholesterolemia by 0.3 to 0.8 years, and T2DM by 0.5 to 1.7 years; lifetime incidence of coronary heart disease would be reduced by 12 to 38 cases per 1000 and stroke would fall by 1 to 13 cases per 1000. They further estimated that the expected lifetime medical care costs due to the 5 diseases included in the study would be reduced by $2200 to $5300 (1996 dollars).[51]

Capturing the effects of weight loss among patients earlier in life upon medical expenditures a decade later was the subject of a study published in 2013 that used Medicare data from 1992 to 2001.[52] The study used a model to estimate Medicare spending for 5 patient populations: no weight loss intervention, 10% or 15% weight loss followed by 90% weight regain over 10 years (temporary weight loss), and permanent 10% or 15% weight loss.[52] The authors found that gross per capita savings to the Medicare program ranged from $6456 to $13,474, depending on BMI at baseline, percent weight loss, and whether the weight loss was temporary or permanent. The results by BMI category are presented in **Table 4**.[52] Weight loss in beneficiaries in the highest BMI category (≥35) was shown to have the greatest impact in terms of cost savings.[52]

Given the increased risk of developing diabetes among persons who are overweight or obese, it is important to establish whether interventions (eg, weight loss) in this population might lessen the risk of progression to diabetes, particularly among those who are at high risk. The Diabetes Prevention Program Research Group evaluated the effects of 2 interventions on the risk of progression to diabetes in a clinical trial that enrolled 3234 adults with a mean BMI of 34.0 (±6.7) and elevated fasting and post-load plasma glucose levels (ie, prediabetes). Participants were randomized to receive a lifestyle modification program, metformin 850 mg twice daily, or placebo. The lifestyle modification program included a low-calorie diet and at least 150 minutes per week of moderate-intensity exercise, with a weight reduction goal of at least 7% of baseline weight.[53] After an average of 2.8 years of follow-up, the incidence of diabetes was 4.8, 7.8, and 11.0 per 100 person-years in the lifestyle modification, metformin, and placebo groups, respectively. The incidence of diabetes was 58% lower among subjects in the lifestyle modification group compared with subjects in the placebo group ($P < .001$); the incidence of diabetes was 31% lower among subjects in the metformin group compared with subjects in the placebo group ($P < .001$). Participants in the lifestyle modification group achieved an average weight loss of 12.3 pounds, participants in the metformin group lost an average of 4.62 pounds, and participants in the placebo group lost an average of 0.22 pounds.[53]

Weight loss also has beneficial effects in patients who have diabetes, as shown in a study by Kumar et al, which found that among 50 patients with T2DM and a mean BMI of 35, the loss of 5% of body weight, resulting from participation in a weight loss program, was associated with a 49% reduction in requirements for antidiabetic medications. Furthermore, 44% (22) of subjects were able to discontinue their anti-diabetic medications altogether, and at the time of discontinuation, a mean weight loss of 11.2% from baseline had been achieved.[54]

Weight loss has also been observed to provide benefits in regard to dyslipidemia and blood pressure, as shown by the results of a 56-week randomized controlled study of 2487 obese patients with cardiovascular risk factors who were treated with a combination of phentermine and topiramate extended-release. A nearly linear relationship between amount of weight lost and degree of improvements in risk factors—including triglycerides, non-HDL cholesterol, systolic blood pressure, and diastolic blood pressure—was observed. For example, subjects who lost between 5% and 10% of body weight experienced a mean 14.5% reduction in triglycerides, and the reduction climbed to 28.7% for subjects who lost between 10% and 15% of body weight. Systolic blood pressure was reduced by 7.5 mm Hg in those losing 5% to 10% of body weight, and was reduced by 10.8 mm Hg among those who lost 10% to 15% of body weight.[55]

Weight loss also benefits patients with sleep apnea. A study of 81 adult patients with sleep apnea and BMI 28 to 40 found that the study intervention (diet and lifestyle changes) reduced the risk of obstructive sleep apnea at follow-up by 65%. The average weight lost was 7.3 kg in the intervention group and 2.9 kg in the control group.[56]

Weight loss also confers benefits in terms of QoL. The immediate and long-term effects of a clinical weight loss program on health-related QoL (HRQoL) in 190 overweight and moderately obese adults were evaluated in a 2-year study conducted by Blissmer et al. HRQoL was evaluated via the SF-36 at baseline, at the conclusion of a 6-month clinical weight loss program, and again at 12 and 24 months post intervention. At 6 months, 144 subjects remained in the study. While baseline scores for bodily pain, vitality, and mental health were poorer among study subjects compared with population norms, after completing the 6-month clinical weight loss program, scores were improved across several domains including physical and mental composite scores as well as subscale scores for physical functioning, general health, vitality, and mental health. Improvements in the mental composite score and the physical functioning, vitality, and mental health subscales were sustained after 24 months.[57]

As described in this section, weight

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loss can improve many obesity-related cardiovascular risk factors, including T2DM, dyslipidemia, and hypertension. These effects are also seen in several measures of health-related quality of life. Benefits are seen with modest weight loss of 5% to 10% of baseline body weight, and additional improvements are seen with greater weight loss.[53-55,57]

Summary

Obesity is a multifactorial condition associated with numerous comorbidities that exact a considerable clinical, quality-of-life, and economic toll. Therapeutic interventions to reduce excess body weight, and consequent associated comorbidities and health risks, are available, effective at promoting weight loss, and cost-effective when evaluated over the short term. Weight loss has been shown to have a positive impact on several comorbidities associated with obesity. Relatively modest weight reductions, from 5% to 10% of baseline body weight, are associated with significant reductions in the risk of developing T2DM among those at high risk for diabetes, as well as significant reductions in the need for antidiabetic medications among those who already have diabetes. Similarly, this degree of weight reduction has been shown to reduce key cardiovascular disease risk factors, including triglycerides, non-HDL cholesterol, and both diastolic and systolic blood pressure. Larger weight reductions result in greater improvement in these risk factors. Treatment options to reduce obesity, and to meaningfully lower its substantial health effects, have been shown to be effective in the short term and should be offered to the increasing number of people who are affected by obesity and who are affected by or are at high risk for its related medical and economic burden. Additional weight loss interventions with long-term efficacy are needed to reduce body weight and maintain weight loss.

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ADA Conference Coverage 2013

Examining the Links Among Sleep-Disordered Breathing, Hyperglycemia, and Poor Outcomes at School

Mary K. Caffrey

For clinicians treating diabetic youth who cannot gain control over glucose levels despite multiple medication changes, it might be time to ask a simple question:

Are you getting enough sleep?

Michelle M. Perfect, PhD, assistant professor in the Department of Disability and Psychoeducational Studies at the University of Arizona, presented findings and recommendations at the 73rd Scientific Sessions of the American Diabetes Association (June 21-25, 2013) in Chicago.

Research in this area—especially among teenagers—is scant, despite concerns about the links that connect sleep, glycemic control and daytime functioning in youth with type 1 diabetes mellitus (T1DM). The findings were first reported in the journal SLEEP.[1]

Yet, according to Perfect, the teenage years are precisely when T1DM patients experience a decline in their adherence to the dietary and management routines needed to keep glucose levels under control. And, like other teenagers, they are likely to be sleep-deprived at a time when rest matters most.

One in 400 youth have T1DM, Perfect said, but at present there are no recommendations for how many hours of sleep a diabetic teen should have. "That's probably because of the lack of data regarding the role of sleep in these youth," she said.

Perfect said prior to her research, there was only 1 other study that specifically examined the relationship between sleep and glycemic control in youth, and that involved pre-pubescent children.[2]

Sleep-disordered breathing is typically associated with obesity, but this study looked at the effects of sleep-disordered breathing, independent of the effects of the youth's body mass index (BMI). Perfect and her co-authors recruited a group of 50 youth aged 10 to 16 years and were able to monitor their sleep through several means: polysomnography, actigraphy, and self-reporting. Sleep-disordered breathing was defined as having an apnea-hypopnea index (AHI) of at least 1.5 events per hour.


Michelle M. Perfect, PhD

Test subjects wore continuous glucose monitors to track A1C levels. Perfect also assessed the test subjects on their daytime sleepiness, depression, and quality of life issues, and asked parents about behavior problems. She also tracked the test subjects' grades, test scores, and school attendance.

Why might poor sleep affect glucose control? As Perfect explained, sleep-disordered breathing leads to fragmented sleep and elevated cortisol; conversely, a portion of non-REM sleep, the "slow wave sleep" or deep sleep, is the restorative period when cortisol levels drop. For youth especially, this is also when a surge in growth hormone occurs.

"They need that slow-wave sleep," she said.

The study's most significant finding was how even minor levels of sleep-disordered breathing were associated with hyperglycemia. Of the 50 test subjects, 14 had sleep-disordered breathing, and this group ended up having average A1C levels 40 points higher than their counterparts (169.52 mg/dL versus 208 mg/dL). Also, Perfect said, the group with sleep-disordered breathing was hyperglycemic more often, more than half the time at 54.17%, compared with 36.64%.

Poor sleep habits were also associated with reduced scores on the quality-of-life measures and on school performance. Test subjects who spent extended periods in the lighter stage of sleep before slow-wave sleep, and less time in that deep sleep, showed not only higher glucose levels, but also behavioral difficulties, lower grades, depression and poorer attendance.

Test subjects with disrupted sleep fared poorly not only when compared with fellow diabetic teens who got better rest, but also when compared with youth in a control group from the Tuscon Children's Assessment of Sleep Apnea Study.

For those who think attention to sleep is not important, Perfect said, "Look at the data, and tell me sleep is not important."

With these results, what should clinicians, educators and parents do? Perfect, whose background is in school psychology, recommended treating the sleep issues (she referred some of her test subjects for treatment). For example, she said, snoring could be an indicator that tonsils and adenoids need to be removed.

Perfect is continuing work in this area with a pilot study at how glycemic control improves when diabetic youth can work to extend their sleep. A 10-year-old boy with A1C at 309 mg/dL was able to bring his blood sugar down 45 points by increasing his sleep by 55 minutes, she said.

"We need to figure out how to get them to go to bed earlier and get them to school."

A controlled study of how extending sleep affects health outcomes, funded by the ADA, was getting under way this summer, Perfect said.

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Accountable Care Organizations

(continued from cover)

said Jeffrey Brenner, MD, founder and executive director of the Camden Coalition of Healthcare Providers.

Under the 2010 Affordable Care Act (ACA), the nation's healthcare system bears financial risk for delivering better care, and the industry is experimenting by rearranging the relationship between those who provide care—doctors, nurses, specialists, and technicians—and those who pay for it, such as insurance companies, major employers who self-insure, and federal and state governments.

ACOs, which integrate care across healthcare providers, are catching on, and ACOs and ACO-like entities operate in as many as 45 states.[1] Between 25 million and 31 million Americans are receiving healthcare services through an ACO, and more than 40% of Americans—126 million people—live in areas with at least 1 ACO, estimate Rick Weil, partner, and Niyum Gandhi, associate partner, in the Health and Life Sciences Practice of the consulting firm Oliver Wyman.

As of November 1, 2012, there were 328 ACOs, up from 221 at the end of May 2012, and 164 in September 2011, according to Leavitt Partners.[2]

While the near-term growth of ACOs seems assured, the jury is still out on the question of whether ACOs can deliver the requisite quality of care to have any measurable impact on long-term costs.

Even if there is no consensus about what quality care entails, initiatives in the marketplace hold clues to the future of how ACOs plan to deliver better care.

Quality and Metrics

Future healthcare quality can't be improved unless hospitals and doctors know how well or poorly they are performing today. It's no surprise, then, that ACOs are sticklers for metrics.

Nationwide Children's Hospital (NCH) in Columbus, Ohio, a sponsor member of the Partners for Kids ACO, which serves more than 300,000 children, tracks its metrics with impressive granularity.

Drug errors, surgical infections, bloodborne infections, and rates of pneumonia associated with ventilator use are reported quarterly and monthly. Even staff compliance with washing hands is plotted on a graph.

The hospital, which serves a pediatric Medicaid population in a 34-county area in central and southeastern Ohio, reports that the number of catheter-associated bloodstream infections has dropped to 0.5-per-1000 catheter days in the first quarter of this year, from an average of 5.1 per 1000 in 2004.

Data collected in separate quality indicators show the hospital doing very well, and that is one measure of better quality. "We try to show metrics of kids getting better," said Kelly Kelleher, MD, vice president of community health at NCH and a research adviser to Partners for Kids.

Kelleher said that fewer children with asthma and neurologic problems have been admitted to NCH's emergency department, and the decline in the rate of pre-term births compared with that of other regions is a sign that the quality of care has improved. "That's how we've improved outcomes," he said.

> *Patient-centered models are designed to help patients maintain an ongoing relationship with the same doctor.*

Even with a 1% decline in the use of neonatal intensive care units (NICUs), multiply that by every child admitted to the NICU at $3000 a day over the course of a year, and the numbers start to add up, he said.

NCH participates in pediatric quality measurement programs promulgated by the Centers for Medicare & Medicaid Services (CMS) and the Agency for Healthcare Research and Quality (AHRQ), and quality measures are set by the government.

For all of NCH's measurements, the question of whether the quality of its care improves the lives of children is, to some extent, one ultimately inferred from the data.

Short of going out and conducting large-scale surveys of families and the progress of their children, which is expensive and not reimbursed by Medicaid, Kelleher said, it's difficult to know if the quality delivered to a child today is truly any better than the care received 5 years ago.

Quality and Providers

Like an anchor tenant in a retail mall, ACOs have traditionally been clustered around big, institutional hospitals.

More recently, it is the doctors' groups that are forming the nucleus of the ACO, as ACOs seek to remain focused on the patient—a key to delivering quality.

Under this model, local primary care doctors, who see their patients regularly and know the family intimately, are in a much better position to determine what is most appropriate for the patient.

Atrius Health, a collection of 7 community-based health groups serving more than 1 million adult and pediatric patients in eastern and central Massachusetts, takes its commitment to improving the quality of care to heart—literally—as quality care "is at the heart of our mission," the Atrius website promises.[3]

Atrius, a Pioneer ACO built on the initiative sponsored by Centers for Medicare & Medicaid Innovation Center, was selected as one of 32 healthcare providers for its ability to deliver "high quality, coordinated care," according to Atrius' website.

Medicare beneficiaries are not locked into a restricted list of providers as are Medicare Advantage patients, or like regular patients were with the managed care networks in the previous generation.

Under the Pioneer ACO model, Medicare beneficiaries seeing doctors who participate in an ACO maintain the ability to see any doctor or healthcare provider, even as they continue to receive the full benefits of Medicare.[4]

Among the medical practices participating under the Atrius brand are 7 primary and multispecialty medical groups, and a hospice care group that delivers care to patients at home.

Atrius' model of delivering quality care was further cemented last year when South Shore Medical Center received the Level 3 Patient-Centered Medical Homes designation from the National Committee for Quality Assurance (NCQA).

Patient-centered models are designed to help patients maintain an ongoing relationship with the same doctor, who leads a team of healthcare experts at a single location, and who takes responsibility or ownership for care of a patient from beginning to end.

The goal with medical homes is to reclaim the importance of the primary care doctor as the gatekeeper to deliver more personalized, coordinated, and efficient care.

Elevating the central role of primary care services instead of more expensive specialty services has been shown to cut hospitalization rates, lower rates of Medicare spending, and improve quality.[5]

Quality and Payers

The 32 Pioneer ACO healthcare organizations were chosen by CMS to test different payment models and to spur competition to deliver higher quality and more affordable care than patients receive now under fee-for-service models.

All 32 ACOs in the program improved quality of care. On the cost side, while

Nationwide Children's Hospital (NCH) in Columbus, Ohio, a sponsor member of the Partners for Kids ACO, which serves more than 300,000 children, tracks its metrics with impressive granularity.

only 13 of the 32 ACOs were able to lower costs, the costs for the entire group of 669,000 beneficiaries in the Pioneer ACOs rose only 0.3% in 2012, less than the 0.8% increase for similar beneficiaries in 2012.[6]

The 13 ACOs produced a savings of nearly $88 million in 2012, partly due to fewer hospital admissions and readmissions, according to a recent study of the Pioneer ACO pilot.[6] Two of the Pioneer ACOs ended up spending more on the beneficiaries than the Medicare fee-for-service model.[6]

Of the 19 Pioneer ACOs that weren't able to cut costs in the first year, 7 announced they would leave the Pioneer program for the Medicare Shared Savings Program model, and 2 more said they would leave the Medicare accountable care arena.[6]

Fee-for-service models have rewarded volume, not the quality of the health services rendered, and have been blamed for driving the cost of healthcare upward, even as there's little evidence that the United States is healthier than nations that spend far less.

Under new payment schemes, hospitals and doctors, for instance, are being asked to take on more risk so that if procedures go awry and patients need to be readmitted, hospitals or doctors don't get reimbursed. The incentive is to get it right the first time, and to penalize mistakes by not paying the bill when things go wrong.

Value-based purchasing, which encourages pay-for-performance, tilts the system in favor of the patient. "The idea is to stimulate the competition among the healthcare system and make health care accountable," said. Jim Frazier, MD, system vice president for medical affairs with Norton Healthcare, an ACO serving Louisville, Kentucky, and southern Indiana. Norton is currently involved in a pilot reimbursement program with the health insurer Humana.

Payment redesign is being structured and recalibrated to take account of providers' readiness to accept financial risk, with health plans, hospitals, and doctors collaborating among themselves to negotiate goals around quality and cost reduction.[7]

Risk-sharing among providers and payers, and bundled payments, are changing the way hospitals and doctors are reimbursed so that the healthcare system moves "from volume to value," said Karen Ignagni, president and CEO of American Health Insurance Plans.[8]

"The challenge is that until the reimbursement (model) is changed, it makes it difficult to make it a true ACO," Frazier said.

Will ACOs and alternative health payment models be enough to control the rising cost of healthcare? The past 3 years have seen healthcare costs level off, but many experts point more to the weak economy as the primary reason, as opposed to structural change within the healthcare system.

Brenner says the nation is in the midst of a 30-year experiment in redefining how to deliver healthcare, and that to succeed at the individual level will mean patients will have to feel cared about and know exactly what happened, why things happened, and how they can prevent their ailments in the future.

For doctors and nurses, it will mean looking forward to taking care of patients and bonding with them every day, he says. At the macroeconomic level, it will mean offering better care at lower costs.

The US healthcare system in still the most expensive in the world by far, and whether the nation achieves better quality by rearranging the provider side or the payment side of the delivery system, "we've got a long way to go," said Brenner.

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Technology: The Artificial Pancreas

Artificial Pancreas

(continued from cover)

NOT JUST 1 DEVICE

The complexity of artificial pancreas systems becomes apparent when considering the 3 types as defined by the US Food and Drug Administration (FDA): (1) threshold suspend devices, (2) control-to-range systems, and (3) control-to-target appliances. Essentially, these divisions relate to how tightly the artificial pancreas tries to maintain appropriate levels.

Threshold Suspend. This type of device is referred to as a "back stop," the mission being to prevent dangerous episodes of hypoglycemia. Once blood glucose levels reach a certain low level, insulin delivery from the pump is suspended. Therefore, for better glycemic control, patients must still check their own blood glucose levels and provide supplemental insulin as needed.

Control-to-Range (CTR). Use of a CTR device is intended to maintain blood glucose levels within a range, actively changing insulin administration once the preset upper or lower limits are reached. In order to obtain optimal control, patients using a CTR system are still required to occasionally check their own levels and administer supplemental insulin as needed.

Control-to-Target (CTT). The system that attempts to achieve the tightest glucose control, the CTT device continually seeks to achieve target levels, day or night. This is the only artificial pancreas unit that is fully automated—the patient should not need to do any glucose monitoring or inject additional insulin.

To help the CTT system achieve target levels, it must do more than add insulin—it may be required to increase sugar levels as well, by injecting glucagon into the body as well. This is referred to as a "bi-hormonal control system."

Source: Types of artificial pancreas device systems. US Food and Drug Administration, November 9, 2012 (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ArtificialPancreas/ucm259555.htm). Accessed August 7, 2013.

Some call it a "closed loop system" or "bionic pancreas," but it is essentially an insulin pump connected to a continuous glucose monitor in a way that the monitor instructs the insulin pump to release (or stop releasing) hormones when needed, to ward off hyperglycemia and avoid hypoglycemia (*See* **Not Just One Device**).

So far, the complexities of such a system have stymied manufacturers' efforts at developing a versatile and reliable product. The ASPIRE trial results,[1] announced in June 2013 at the American Diabetes Association (ADA) meeting in Chicago, signaled strong progress in this area—and maybe the beginning of the end of the journey. Patients using the investigational device had a 32% lower incidence of nocturnal hypoglycemia episodes compared with those using insulin pumps alone. Take note: The investigational product was tested against state-of-the-art treatment.

Also in June, Medtronic reported that it was beginning a trial of its "third-generation, fully automated artificial pancreas system" to test whether its use can prevent nocturnal hypoglycemia.[2] This "control-to-target" device seems to be in its final stages prior to FDA submission. If successful, it and artificial pancreas systems by other makers, could be a boon to patients whose glucose levels are extremely difficult to control.

For payers, it raises rather complex questions: What will it cost? How can we pay for the technology for the patients who need it most? Insulin pumps average around $7000 plus $250 for monthly supplies. This implies the challenge: How much utilization can be expected? More than 300,000 patients today are estimated to use insulin pumps (and perhaps 10% of these have type 2 diabetes mellitus).[3] Interestingly, according to a 2010 article, more patients with T1DM in the United States use insulin pumps than insulin pens.[4]

From the manufacturer's point of view, the challenges of coverage remain secondary to the challenges of bringing the technology to the FDA finish line. Max Gill, MBA, senior director of health economic policy and reimbursement at Medtronic Diabetes, explained, "As we progress toward these goals, we are

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committed to partnering with payers to ensure access for people with diabetes." He predicted that "For those devices with therapy automation but not a fully 'closed loop' artificial pancreas system, we anticipate that payers will follow existing coverage policies for external insulin pump therapy and continuous glucose monitoring."

Lessons of the (Recent) Past

To better consider how health plans and insurers may decide to cover an artificial pancreas system, it may be best to start with its key individual components, the pump and the continuous glucose monitor. Historically, health plans and insurers moved cautiously in covering both components.

Payers (private and public) have clearly defined policies on whether they cover insulin pumps, to what extent, and what restrictions (ie, preauthorization criteria) may affect eligibility. These policies are based on decades of experience with the device. Their experience indicates that patients who use insulin pumps optimally are highly motivated to tightly control their glycemic levels and are committed to frequently checking their blood glucose levels throughout the day. Clearly, insulin pumps are not for every patient. In addition, the devices themselves, though becoming smaller and less conspicuous over the years, are still a bit ungainly.

"For many medical devices, there is a significant lag time between FDA approval and health plan benefit coverage," said Allan Chernov, MD, medical director, Blue Cross Blue Shield of Texas. This provides plans and insurers a window in which to gain experience both in terms of utilization and clinicians in using the technology. Yet, state mandates on diabetes coverage may limit how plans can manage the utilization of this technology **(Figure)**. Private payers have by and large been required by state insurance commissioners or departments of insurance to make insulin pumps available under mandates to provide benefits to patients with diabetes **(Figure)**. Only Alabama, Idaho, North Dakota, and Ohio do not require this coverage. Mississippi, Missouri, and Washington require that the coverage be offered. All other states mandate the coverage.[5]

Chernov explained, "For diabetes, many states—including Texas—have quite broad mandates for coverage of diabetes treatment, equipment, and supplies, which means we'll probably see early adoption after FDA approval, at least in fully insured plans. Many administration-service only plans, usually those of smaller companies, will act in the same way as fully insured plans (including mandates)." On the other hand, plans that were not as bound to state mandates, like ERISA plan sponsors, may take a different view. He said, "The large, national self-insured companies are more likely to be conservative about adopting high-cost technology with limited long-term outcome data."

Coverage of the second major component—continuous glucose monitoring—is fairly consistent among health plans (**Table 1**). A survey by the Juvenile Diabetes Research Foundation (JDRF) found that most major plans offer coverage, with the greatest restrictions being the need to demonstrate difficulty in reaching or maintaining goal glycemic levels, or "hypoglycemia unawareness" (or a patient's inability to quickly recognize the onset of hypoglycemia and take appropriate action).[6]

Public Coverage Scenarios

However, even if one lives in a state with mandated coverage, out-of-pocket cost requirements (eg, in high-deductible plans) could mean that the patient will be picking up a large portion of them in a private plan. This also may apply to Medicare.

According to the Centers for Medicare & Medicaid Services (CMS), a physician's prescription for an insulin pump is covered under part B durable medical equipment, entitling the patient to 80% coverage, as long as the pump is obtained through a Medicare-approved supplier. The patient would be liable for the remaining 20% as well as the Medicare Part B deductible, if this is not covered by supplemental insurance. Medicare has some requirements as well for patients to obtain the pump, such as having a lab test showing little or no ability to naturally produce insulin and having been using multiple daily injections for more than 6 months. Also, patients who were using a pump before becoming Medicare eligible automatically fulfill the requirements upon reaching Medicare eligibility. Medicare also covers continuous glucose monitoring systems, assuming the patient meets eligibility criteria.

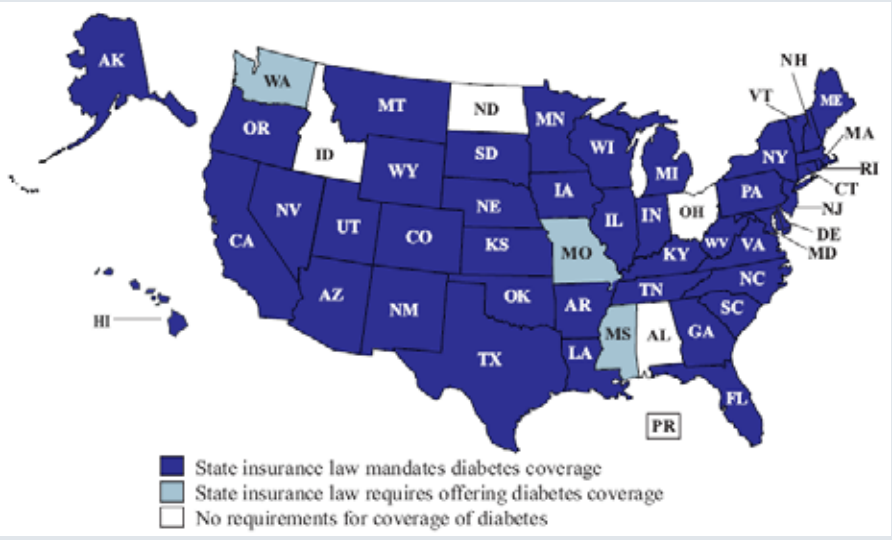
For Medicaid, a survey by the Kaiser Family Foundation revealed that restrictions applying to insulin pumps could be found only in Arizona (uncovered), Arkansas (medical supplies limited to $250 per month), and Pennsylvania (limited to home health care benefit only).[7] In nearly all state Medicaid programs, prior authorization and other eligibility criteria would have to be met to receive coverage.

It is worth noting that of the states moving forward with Medicaid expansion (24 confirmed as of July 1, 2013),[8] technologies like the artificial pancreas system (and even insulin pumps and continuous glucose monitors) could pose significant short-term cost challenges, not considering potential longer-term savings from avoidance of diabetes-related complications.[9]

Even states that cover insulin pumps will have restrictions that could affect populations who might benefit from artificial pancreas systems. Janet Sullivan, MD, medical director of the Hudson Health Plan, Tarrytown, New York, told *Evidence-Based Diabetes Management* that "New York State Medicaid covers insulin pumps when medically necessary. The State may make a [separate] decision about coverage of the new technology." She emphasized, "If New York State decides the technology should be a benefit under the Medicaid program, or has not yet made a determination, coverage will still require prior authorization for medical necessity. Denials of investigational technology are subject to external appeal in New York."

Viewing this from another angle, of the 10 states with the highest incidence of diabetes (type 1 and type 2), only 2 are moving forward with Medicaid expansion (another, Tennessee, is trying

Figure. State Diabetes Coverage Requirements Within Private Insurance



Reprinted from Providing Diabetes Health Coverage: State Laws & Programs. National Conference of State Legislators. May 2011. (http://www.ncsl.org/issues-research/health/diabetes-health-coverage-state-laws-and-programs.aspx). Accessed August 21, 2013.
Map data updated December 2009 based on NCSL research.

Table 1: Coverage Policies for the Long-Term Use of Continuous Glucose Monitoring Devices

Plan	CGM Coverage Policy
Aetna	Covered for all patients with T1DM ≥ 25 yr and those < 25 yr with recurrent severe hypoglycemia
BCBS of Massachusetts	Covered for patients with T1DM with recurrent unexplained severe hypoglycemia or those who are pregnant
BCBS of Illinois	Covered for patients with T1DM ≥ 25 yr
Group Health Co-op of Puget Sound	No formal coverage
Humana	Covered for patients with inadequate glycemic control (despite ≥ 4 fingersticks/day) or recurrent severe hypoglycemia despite modifications to insulin regimen or unawareness of hypoglycemia
Kaiser Permanente	Covered for patients with T1DM
UnitedHealthcare	Covered for patients with T1DM not achieving glycemic goal or those with hypoglycemia unawareness

T1DM indicates type 1 diabetes mellitus.
Adapted from: Artificial pancreas project. Juvenile Diabetes Research Foundation December 2011 (http://artificialpancreasproject.com/about/insurance.html). Accessed August 15, 2013.

Table 2: Medicaid Expansion Plans for Top 10 States with Diabetes Incidence in Adults

State	Diabetes Incidence	Status of Medicaid Expansion
Mississippi	11.3%	Not moving forward
Alabama	11.1%	Not moving forward
West Virginia	10.7%	Moving forward
Louisiana	10.3%	Not moving forward
Tennessee	10.2%	Developing a program
Oklahoma	10.1%	Not moving forward
Kentucky	10.1%	Moving forward
South Carolina	9.9%	Not moving forward
Texas	9.8%	Not moving forward
Georgia	9.8%	Not moving forward

Sources: Diabetes report card, 2012. Centers for Disease Control and Prevention 2012 (http://www.cdc.gov/diabetes/pubs/pdf/diabetesreportcard.pdf). Accessed August 22, 2013; and Status of state action on Medicaid expansion Kaiser Family Foundation, July 1, 2013 (http://kff.org/medicaid/state-indicator/state-activity-around-expanding-medicaid-under-the-affordable-care-act/). Accessed August 23, 2013.

to create its own program to expand Medicaid; this may require a waiver from the federal government) (**Table 2**).[8,10] What needs to be avoided, most agree, is the unintended creation of a 2-tier system, in which some states decide to cover the new technology and some do not (ie, the "haves" and "have nots"). It does not seem at this point, before the marketing of the artificial pancreas system at least, that this will be the case.

Chernov stated that "In Texas, Medicaid covers insulin pumps conditionally for patients with type 1 diabetes who meet criteria, primarily related to documented wide blood glucose fluctuations and poor control. I think it's safe to assume that even with mandated coverage, there will be an ability to set medical necessity criteria for an artificial pancreas. There may not be mandatory prior authorization, but it's pretty much standard practice in the provider community now to request pre-service clinical review for high cost services rather than risk post-service claim denials. This *de facto* voluntary process works better than mandatory prior authorization although generally the same appeal rules and regulations apply to adverse decisions from voluntary pre-service clinical review."

More Than the Sum of Its Parts?

Some health plans will be considering the artificial pancreas device from a perspective different from that of insulin pumps. Rather than an evolution of insulin pump technology, they may consider an artificial pancreas as an entirely new device, reflecting their much more complicated nature. In that case, would they be priced as more than the "sum of their parts?"

For example, SelectHealth in Salt Lake City will view the artificial pancreas as completely new technology, according to Medical Director Kenneth Schaecher, MD. "This will require a separate technology assessment and would not be covered simply as another insulin pump," he said. Ultimately, he believes, "coverage will depend upon evidence demonstrating not only improved health outcomes—both short and long term—but also cost effectiveness and medical cost offsets related to medical resource utilization, such as hospitalization and emergency room visits for hypoglycemia."

This bionic or artificial pancreas is clearly a powerful evolutionary technological step. Until regenerative bioengineering can synthetically produce an organ with human beta cells that would wholly replace the pancreas of a patient with T1DM, these closed loop systems represent today the closest thing to automatic pancreatic insulin regulation.

The science and engineering moves forward. Perhaps hundreds of thousands of patients—private and public; many with type 1 disease, some with type 2—may want a sip from this holy grail when it is finally revealed. Will coverage of the technology be able to quench the thirst?

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Policy: Effect on Payers

Obesity Declaration

(continued from cover)

cans," said AMA board member Patrice Harris, MD. "The AMA is committed to improving health outcomes and is working to reduce the incidence of cardiovascular disease and type 2 diabetes, which are often linked to obesity."[1]

The policy is a sea change for the AMA and long awaited by obesity physicians and advocates. In 2009, the Board of Delegates voted not to recognize obesity as a disease for determining disability. But this year, on the same day AMA announced the obesity policy, it separately announced complementary policies recognizing potential risks of prolonged sitting and encouraging the removal of sugar-sweetened drinks from the Supplemental Nutrition Assistance Program (SNAP).[7]

"This has tremendous symbolic importance," said Ted Kyle, RPh, MBA and chair of the advocacy committee of The Obesity Society, whose more than 2000 members are active in basic and clinical obesity research. "The NIH adopted these guidelines in 1998, so it took AMA a long time to come around."

Obesity, perhaps unique among ailments, was commonly called an epidemic before it was officially classified a disease. According to the Centers for Disease Control and Prevention (CDC), 35.7% of adults and 17% of children are considered obese,[8] with the obesity rate among teens and children having tripled since 1980.[8] CDC estimated medical costs attributable to obesity in 2008 at $147 billion, with per capita spending on obese persons $1,429 more than persons of healthy weight.[9]

John Morton MD, associate professor of surgery at Stanford University and secretary-treasurer of the American Society for Metabolic and Bariatric Surgery, said while AMA is last among medical associations and public health organizations to call obesity a disease, it is the most influential.

"The AMA recognizing obesity is a disease has practical implications that cannot be overstated," Morton said. "Some insurers might decide to cover it. This encourages us to look at obesity from a treatment model. Prevention is the first thing. I believe this will get people thinking (whether) advertising sugar to children is the right thing to do. This will open up discussion in the family, which is good because obesity is a family disease."

A 2004 Gallup poll found only 21% of Americans considered obesity a disease, while 75% of those polled, including those who were obese or overweight, viewed it as a problem resulting from poor eating and lifestyle habits.[10] A Gallup representative said the firm will consider posing the question again. The AMA policy change can only help reduce that stigma of obesity, Kyle said.

"A lot of folks were clinging to old notions that obesity is a matter of choice," Kyle said. "Folks who study this disease know there is complex biology going on. Choices matter, but that is not all that matters. Two people can eat

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the same diet and have much different weight.''

A clause in the resolution supporting the new AMA obesity policy implicitly addressed bias, reading, "The suggestion that obesity is not a disease but rather a consequence of a chosen lifestyle exemplified by overeating and/or inactivity is equivalent to suggesting lung cancer is not a disease because it was brought about by individual choice to smoke cigarettes.''

The AMA policy change adds momentum to the recognition of obesity as a disease that requires treatment and the means to obtain treatment. As an example, in 2004, then-Secretary of Health and Human Services Secretary Tommy G. Thompson, testifying before a Senate subcommittee, called obesity "a critical public health problem in our country that causes millions of Americans to suffer unnecessary health problems and to die prematurely." Thompson announced Medicare would strip language from its policies that did not characterize obesity as a disease to remove barriers to necessary obesity coverage.

Nine years later, and the same day the AMA delegates voted on the new obesity policy, federal lawmakers cited the AMA action when they announced introduction of the Treat and Reduce Obesity Act of 2013. The law, introduced by US Senators Tom Carper, D-Delaware, and Lisa Murkowski, R-Alaska, and US Representatives, Bill Cassidy, R-Louisiana, and Ron Kind, D-Wisconsin, would require the Centers for Medicare & Medicaid Services (CMS) to "highlight and provide additional information regarding Medicare coverage'' of obesity treatments and medication coverage, goals much like those Thompson had reached for in 2004.

Indeed, news reports in the immediate aftermath of the AMA vote predicted the policy change would be a boon for new obesity drugs and those under development, notably Belviq from Eisai and Arena Pharmaceuticals and Qsymia, sold by Vivus. Another company, Orexigen, is working toward FDA approval for Contrave, which is a combination of bupropion and sustained-release naltrexone.[11]

There is no sign that health insurers will suddenly be more willing to pay for obesity treatments, especially surgery, in the wake of the AMA policy. Susan Pisano, spokeswoman for America's Health Insurance Plans (AHIP), the national trade association of health insurers, said the AMA reclassification by itself would not change how insurers view obesity.

"Whether you call obesity a risk factor, a condition or a disease, coverage is determined by what is a safe and effective treatment or service,'' Pisano said. "What drives coverage is evidence that a treatment or service is safe and effective."

What drives coverage decisions is far from clear to Ethan Lazarus, MD, director of Clinical Nutrition Center, an obesity medicine practice in Denver, Colorado, that performs bariatric surgery. "Until now insurance companies could sit by and say this (obesity) is not a disease and not pay for treatment, even though people are dying from this disease at an alarming rate,'' said Lazarus, who spoke in favor of the policy during the AMA debate as delegate from the American Society of Bariatric Physicians.

News reports in the immediate aftermath of the AMA vote predicted the policy change would be a boon for new obesity drugs and those under development, notably Belviq from Eisai and Arena Pharmaceuticals and Qsymia, sold by Vivus.

Lazarus cited the case of a recent new patient, an obese a 39-year old father of 2 young children. He was suffering congestive heart failure, type 2 diabetes mellitus, sleep apnea, depression, and psoriasis. The man's cardiologist advised bariatric surgery, but his insurance company would not pay for surgery and stopped him from paying for it, according to the patient.

"I was told that if I paid for the surgery myself that I would not be covered medically for any complications that may arise from the surgery for (my) lifetime,'' the patient, who asked for anonymity, wrote in an e-mail. "Given my diabetes and CHF I am at a higher risk for complications and the fact that they said for lifetime, who knows what they would blame on the after effects of the surgery and deny me coverage.''

Lazarus said he's hopeful the AMA recognition of obesity as a disease will eventually lead to a standard criteria for health insurance to cover surgery but also systemic changes. "This resolution is saying we should treat the obesity as we do the high blood pressure,'' he said. "There needs to be coverage and medical school education. I am a board-certified physician and I got 4 lectures on nutrition and none on obesity in medical school.''

Shortly after the vote, the AMA view of obesity as a disease had legal significance. An employee of Car-Mart Inc in Missouri filed suit in federal court claiming he'd been fired for being "severely obese'' in violation of the American with Disabilities Act (ADA), the first time obesity has been cited in an ADA suit.[12]

Jon Hyman, a Cleveland employment law attorney with Kohrman Jackson & Krantz specializing in the American with Disabilities Act, said the prestige of the AMA will inevitably makes its view on obesity a factor in disability claims.

"That is the trade association of physicians, and when they speak or offer an opinion, people tend to listen,'' he said.

LuAnn Heinen, vice president at the National Business Group on Health, based in Washington, DC, said employers shouldering the costs of health insurance have long been focused on obesity.

"By itself the AMA action doesn't mean that much for employers because they have been concerned about the issue for a long time,'' Heinen said. "It improves the ability to analyze claims data because obesity is now coded. We are worried it might be used to drive more use of medical services when the message we need is to change our lifestyle and choices. Bariatric surgery is a covered benefit, but everybody would prefer it wasn't needed, which is why many companies use Weight Watchers, online coaching, various incentives and benefits.''

Many observers view the AMA's obesity declaration as momentous, similar to its 1956 recognition of alcoholism as a disease or the Surgeon General's warning on cigarettes in 1964. Neither action had immediate consequence or was binding on anyone. But both events proved to be turning points, after which there was a gradual shift in thinking: Instead of the conditions being viewed as the actions of individuals with health consequence, they were recognized as matters of treatment and public health.

"This (designation of obesity as a disease) is not on our radar screen among current issues but we're aware of it,'' said Jason Hammersla, director of communications for the American Benefits Council. He noted employers and insurers evolved substance abuse and mental health benefit packages for decades before the Mental Health Parity and Addiction Equity Act of 2008 required group health plans to treat mental health and substance abuse disorders on par with physical illness.

"There is a long gestation period on something like this,'' Hammersla said.

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