A SPECIAL SUPPLEMENT ON
Hot Topics in Primary Care

- Individualizing Dual Therapy for Type 2 Diabetes Mellitus  S4
- Community-Acquired Bacterial Pneumonia: Is There Anything New?  S10
- Cardiovascular Safety of Medications for Type 2 Diabetes Mellitus  S16
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Hot Topics in Primary Care

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# Hot Topics in Primary Care

## Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>S3</td>
</tr>
<tr>
<td>Stephen A. Brunton, MD, FAAFP</td>
<td></td>
</tr>
<tr>
<td>Individualizing Dual Therapy for Type 2 Diabetes Mellitus</td>
<td>S4</td>
</tr>
<tr>
<td>Neil S. Skolnik, MD; Florence Jaffa, DO; and Yan Kiriakov, DO</td>
<td></td>
</tr>
<tr>
<td>Community-Acquired Bacterial Pneumonia: Is There Anything New?</td>
<td>S10</td>
</tr>
<tr>
<td>Hans Liu, MD, FACP</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Safety of Medications for Type 2 Diabetes Mellitus</td>
<td>S16</td>
</tr>
<tr>
<td>Javed Butler, MD, MPH, MBA</td>
<td></td>
</tr>
<tr>
<td>Demystifying the Differences: Follow-on Biologics, Biosimilars, and Generics</td>
<td>S22</td>
</tr>
<tr>
<td>Eugene E. Wright, Jr., MD; Thomas C. Blevins MD, FACE, FNLA, ECNU; Beverly Reed, MSN; and Roy Daniel Pollom, MD</td>
<td></td>
</tr>
<tr>
<td>Titratable Fixed-Ratio Combinations in Type 2 Diabetes Mellitus:</td>
<td>S28</td>
</tr>
<tr>
<td>Focus on GLP-1R Agonists Combined With Basal Insulin</td>
<td></td>
</tr>
<tr>
<td>James LaSalle, DO, FAAFP; and John R. White, Jr., PA-C, PharmD</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of Cirrhosis and Evaluation of Hepatic Encephalopathy:</td>
<td>S34</td>
</tr>
<tr>
<td>Common Errors and Their Significance for the PCP</td>
<td></td>
</tr>
<tr>
<td>Steven L. Flamm, MD</td>
<td></td>
</tr>
<tr>
<td>Role of the Microbiome in Disease:</td>
<td>S40</td>
</tr>
<tr>
<td>Implications for Treatment of Irritable Bowel Syndrome</td>
<td></td>
</tr>
<tr>
<td>Brian E. Lacy, PhD, MD</td>
<td></td>
</tr>
<tr>
<td>Medication Adherence in Type 2 Diabetes Mellitus:</td>
<td>S46</td>
</tr>
<tr>
<td>Real-World Strategies for Addressing a Common Problem</td>
<td></td>
</tr>
<tr>
<td>Stephen A. Brunton, MD, FAAFP; and William H. Polonsky, PhD, CDE</td>
<td></td>
</tr>
<tr>
<td>The Cardiovascular Safety of Nonsteroidal Anti-Inflammatory Drugs:</td>
<td>S52</td>
</tr>
<tr>
<td>Putting the Evidence in Perspective</td>
<td></td>
</tr>
<tr>
<td>Martin Quan, MD</td>
<td></td>
</tr>
<tr>
<td>Sublingual Immunotherapy: A Guide for Primary Care</td>
<td>S58</td>
</tr>
<tr>
<td>Eli O. Meltzer, MD</td>
<td></td>
</tr>
</tbody>
</table>

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Introduction
Stephen A. Brunton, MD, FAAFP

The rapidly evolving management of myriad diseases encountered in primary care makes it challenging for the family physician to provide optimal evidence-based patient care. The goal of this supplement is to help family physicians address some of these challenges by offering the insights of fellow physicians who have extensive experience with these management issues.

The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial was intended to provide greater clarity regarding the cardiovascular safety of nonsteroidal anti-inflammatory drugs. Study limitations have important implications for primary care.

Alterations in the human microbiome are increasingly recognized as contributing to human disease. Treatments that target the gut microbiota are proving useful for patients with irritable bowel syndrome, as well as cirrhosis and hepatic encephalopathy. Early recognition of cirrhosis in primary care is essential to slow disease progression.

Although not much has changed in the management of patients with community-acquired bacterial pneumonia over the past decade, there are new developments on the horizon with the anticipated release of new treatment guidelines, as well as new antibiotics.

The provision of immunotherapy is a modality that has not been accessible for most family physicians. Four products recently became available in the United States that allow for allergen immunotherapy via the sublingual route. Offering similar efficacy as subcutaneous immunotherapy, these sublingual products have important benefits that make them useful for managing grass, pollen, and dust mite allergies in primary care.

As physicians on the front line managing the pandemic of diabetes, numerous advances allow greater opportunity to individualize care and improve patient outcomes. This includes new medication classes as add-on therapy to metformin such as the dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists that act on the incretin system, and the sodium glucose cotransporter-2 inhibitors that act on the kidney. These medications—particularly the glucagon-like peptide-1 receptor agonists—are recommended as an alternative to prandial insulin for patients with type 2 diabetes mellitus with inadequate glycemic control with basal insulin. An important consideration in selecting therapy in patients with type 2 diabetes mellitus is medication safety. The results of several of the many clinical trials assessing their cardiovascular safety have recently been published with important implications for patient management.

Another option for the management of patients with diabetes mellitus has become available with the approval of the follow-on biologic insulin glargine in the United States. Meeting more stringent regulatory standards, there are important differences between follow-on biologics and generic small-molecule medications. Along with implementation of the Necessity-Concerns Framework and shared decision-making as part of effective patient-provider communication, new drugs and drug delivery systems for diabetes have become available (with more on the horizon) to address key patient barriers related to medication adherence.

I hope you find Hot Topics in Primary Care helpful as you continue to provide the highest quality of care for your patients.

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Individualizing Dual Therapy for Type 2 Diabetes Mellitus

Neil S. Skolnik, MD; Florence Jaffa, DO; and Yan Kiriakov, DO

INTRODUCTION

While many advances in the management of patients with type 2 diabetes mellitus (T2DM) have occurred over the past decade, nearly half of patients with diabetes still have a glycated hemoglobin (HbA1c) above the target of 7.0%.

The combination of lifestyle management with or without metformin is recommended as initial treatment for patients with newly diagnosed T2DM in the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) guidelines. Metformin is the recommended first-line medication based on efficacy, safety, and cost. It can take 2 years to intensify therapy when patients are not at goal on a single medication. Timely treatment intensification has been shown to be important for those who do not achieve their individualized target HbA1c level.

OPTIONS FOR INTENSIFYING METFORMIN MONOTHERAPY

The 2015 ADA/EASD position statement recommends that the decision about which medication to use next after metformin be individualized based on 5 primary characteristics of the medications: efficacy, risk of hypoglycemia, effect on weight, side effects, and costs. The 6 classes recommended with equal preference are: dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide-1 receptor agonist (GLP-1RA), insulin (basal), sodium-glucose cotransporter-2 (SGLT-2) inhibitor, sulfonylurea (SU), and thiazolidinedione (TZD).

In contrast, the 2016 American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) algorithm suggests a hierarchy of usage after metformin in the following order from highest to lowest preference: GLP-1RA, SGLT-2 inhibitor, DPP-4 inhibitor, TZD, and basal insulin as the top 5, while individualizing decisions. Clearly defining the desired characteristics of a potential second-line medication and understanding how each medication class fits with regard to these characteristics will facilitate selecting treatment for an individual patient. This review summarizes the clinical characteristics of the antihyperglycemic medication classes recommended by the ADA/EASD and AACE/ACE guidelines.

Ideal attributes for second-line therapy

While it is clear that medication choices need to be individualized to a patient’s needs, interests, and capabilities, certain characteristics can be considered as desirable in a second-line medication. These characteristics include high efficacy (ie, a meaningful effect on HbA1c), weight loss instead of weight gain, low risk of hypoglycemia, favorable cost, tolerable side effect and adverse event profiles, and good glycemic durability (length of time treatment maintains glycemic control at maximally tolerated doses).

SULFONYLUREAS

SUs remain widely used in combination with metformin because of their complementary mechanism of action, efficacy in lowering HbA1c, and low cost. The addition of an SU to metformin reduces HbA1c ~1%. The United Kingdom Prospective Diabetes Study 33 (UKPDS 33) demonstrated that intensive glycemic management with either an SU or basal or basal-bolus insulin decreased risk of microvascular complications over 10 years, with macrovascular benefit emerging after an additional 10 years of follow-up.

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### TABLE  Key attributes of selected antihyperglycemic medications

<table>
<thead>
<tr>
<th></th>
<th>SU1-10</th>
<th>TZD11,12</th>
<th>SGLT-2 inhibitor13-15</th>
<th>DPP-4 inhibitor16-19</th>
<th>GLP-1RA16-25</th>
<th>Basal insulin16-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c reductionb</td>
<td>–1%</td>
<td>0.4%-0.9%</td>
<td>0.5%-1%</td>
<td>0.4%-0.5%</td>
<td>0.5%-1.3%</td>
<td>Theoretically unlimitedc</td>
</tr>
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<td>Glycemic durability</td>
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<td>++/++++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Effect on weight</td>
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<td>↑</td>
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<tr>
<td>Other safety concerns</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonamide hypersensitivity (glim, glyb); hypoglycemia; hypersensitivity reactions; hemolytic anemia; weight gain</td>
<td>Heart failure; ischemic CV events (rosi); hepatic failure; bladder cancer (rosi); edema/weight gain; fractures; macular edema; decreased hemoglobin/hematocrit; hypoglycemia with SU or insulin</td>
<td>Severe renal impairment, ESRD, dialysis; hypotension; ketoacidosis; acute kidney injury; renal impairment; hyperkalemia (canan); urosepsis/pyelonephritis; genital mycotic infection; ↑LDL-C; bladder cancer (dapa); bone fracture; hypoglycemia with SU or insulin</td>
<td>Acute pancreatitis; acute renal failure (sita); allergic/hypersensitivity reactions; arthralgia; heart failure (saxa, alo); hepatic failure (alo); hypoglycemia with SU or insulin</td>
<td>Medullary thyroid cancer (alb, dula, ex QW, lira); multiple endocrine neoplasia syndrome (alb, dula, ex QW, lira); thyroid C-cell tumors (alb, dula, ex QW, lira); pancreatitis; renal impairment; gastroparesis (alb, dula, ex QW, lix); hypersensitivity reactions; injection-site reactions (ex QW); hypoglycemia with SU or insulin; nausea, vomiting, diarrhea</td>
<td>Hypoglycemia; hypokalemia; allergic reactions; fluid retention with TZD</td>
<td></td>
</tr>
</tbody>
</table>

| Risk of hypoglycemia | Moderate | Low | Low | Low | Low | High |
| Cost | Low | Low | High | High | High | High |

Abbreviations: alb, albiglutide; alogliptin; cana, canagliflozin; CV, cardiovascular; dapa, dapagliflozin; DPP-4, dipeptidyl peptidase-4; dula, dulaglutide; ESRD, end-stage renal disease; ex QW, exenatide once weekly; glim, glimepiride; GLP-1RA, glucagon-like peptide-1 receptor agonist; gly, glyburide; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; lira, liraglutide; lix, lixisenatide; rosi, rosiglitazone; saxa, saxagliptin; SGLT-2, sodium-glucose cotransporter-2; sita, sitagliptin; SU, sulfonylurea; TZD, thiazolidinedione.

aSee text for differences, if any, among medications within the same class. Data are not based on head-to-head comparisons.

bAs add-on therapy to metformin.

+ = limited; ++ = good; +++ = excellent.

↓ = decrease; ←→ = no change; ↑ = increase.

However, the effects of SUs on macrovascular complications are currently an area of controversy.30,32 In older adults, shorter-acting SUs, such as glipizide, are preferred over longer-acting agents, such as glyburide, which have considerably greater risk for hypoglycemia.33

Limitations of SUs include an average weight gain of 2.2 kg, moderate risk for hypoglycemia, and limited glycemic durability.30,34 A meta-analysis found a higher risk for hypoglycemia with the addition of an SU compared with the addition of a DPP-4 inhibitor, GLP-1RA, SGLT-2 inhibitor, or TZD.32 These limitations are reflected in the AACE/ACE guidelines citing a lower preference for SUs.7,30

### THIAZOLIDINEDIONES

TZDs are moderately effective in lowering HbA1c when used in combination with metformin.35,36 Addition of a TZD to metformin reduces HbA1c ~0.9%.30 TZDs have a low risk of hypoglycemia and are associated with improvements in high-density lipoprotein cholesterol and triglyceride levels.2 In addition, rosiglitazone has demonstrated superior glycemic durability over a median of 4 years compared with metformin or glyburide.37

The limitations with TZDs lie in their side effect profile, including peripheral edema and weight gain.30 Rosiglitazone is no longer widely used because of eventually unsubstantiated concerns of increased cardiovascular (CV) risk.38,39 In contrast, pioglitazone may reduce the risk for the composite of death, myocardial infarction (MI), or stroke, and recently has been shown to decrease the risk for recurrent stroke in patients with insulin resistance without diabetes who have had a transient ischemic attack or minor, nondisabling ischemic stroke.40,41 TZDs increase the risk for heart failure...
GLP-1 RECEPTOR AGONISTS

Addition of a GLP-1RA to metformin reduces HbA1c 0.5% to 1.3%.30 Severe hypoglycemia is a rare event.49-54 Weight loss, averaging 2 kg to 5 kg when a GLP-1RA is added to metformin, may be important to some patients,30,49-55 although the need to inject GLP-1RAs may be a barrier for others. Delayed gastric emptying is more pronounced with the short-acting GLP-1RAs exenatide twice daily and lixisenatide, which likely contributes to their greater effects on postprandial glucose (PPG).56,57 The longer-acting GLP-1RAs (albiglutide, dulaglutide, exenatide once weekly, and liraglutide) provide more sustained effects on the 24-hour glucose level and have minimal impact on gastric motility, resulting in a greater effect on fasting plasma glucose (FPG) and greater reduction of HbA1c than short-acting GLP-1RAs.58

Improvements in various markers of β-cell function have been reported in patients with T2DM treated with a GLP-1RA, which suggests that they may have good durability of response.56,60 In fact, a recent meta-analysis concluded that glycemic durability with the addition of a GLP-1RA to metformin was comparable to the addition of an SGLT-2 inhibitor and greater than the addition of a DPP-4 inhibitor, TZD, or SU over 24 weeks to 76.8 months of follow-up.32

Another potential benefit of GLP-1RAs is a modest reduction in systolic (0 mm Hg to 6 mm Hg) and diastolic (0 mm Hg to 4 mm Hg) blood pressure, with no significant differences appreciated among the GLP-1RAs.30,49,51-53,55,61 Additionally, a reduction in the blood triglyceride level has been observed at the lumbar spine, femoral neck, and hip.43,45

An association between TZDs and bladder cancer continues to be controversial.46 The ADA/EASD has concluded, “Earlier concerns that the TZDs—in particular pioglitazone—are associated with bladder cancer have largely been allayed by subsequent evidence.”2,47 In contrast, the US Food and Drug Administration (FDA) announced in December 2016 that it has concluded that use of pioglitazone may be linked to an increased risk for bladder cancer.48

DPP-4 INHIBITORS

Key positive features of the DPP-4 inhibitor class of medications are safety and tolerability. The risk for overall, mild, moderate, total, or severe hypoglycemia with the combination of a DPP-4 inhibitor and metformin is low and similar to that with metformin monotherapy.30,67-70 Additionally, the incidence of abdominal pain, nausea, and vomiting is generally similar when comparing the combination of metformin and DPP-4 inhibitor with metformin monotherapy.30 DPP-4 inhibitors have been associated with a neutral effect on weight and a low incidence of hypoglycemia.30,67-70 They have lower efficacy in HbA1c reduction than some other agents30,67-70 providing modest reduction of HbA1c of 0.5% to 0.65% when added to metformin.30

DPP-4 inhibitors have been shown to improve several markers of β-cell function.71-74 Limited data suggest less favorable improvement in β-cell function associated with the DPP-4 inhibitors compared with GLP-1RAs.75 Recent CV outcomes trials showed no increase in the risk of MACE with alogliptin, saxagliptin, and sitagliptin.76-78 An FDA analysis of these studies concluded that there is a 20% to 25% increased risk of hospitalization for heart failure with alogliptin and saxagliptin.79
As with the GLP-1RAs, a question of increased risk for pancreatitis and pancreatic cancer has been raised, with conflicting conclusions.80-83

SGLT-2 INHIBITORS

The addition of an SGLT-2 inhibitor to metformin results in an ~0.5% to 1.4% reduction in HbA1c.84-89 It also confers a low risk of hypoglycemia, with an incidence that appears to be the same or only slightly higher than that with metformin alone.30,90 Additional reduction in body weight averaging 1 kg to 4 kg has been observed following the addition of an SGLT-2 inhibitor to metformin.30,84-88 The addition of an SGLT-2 inhibitor to metformin reduces systolic blood pressure an average of 4 mm Hg compared with metformin alone.30

SGLT-2 inhibitor therapy increases β-cell insulin secretion and increases insulin sensitivity; improvement in β-cell function appears to result from reduced hyperglycemia.90-92 SGLT-2 inhibitors have demonstrated sustained glycemic control over 2 years as add-on therapy to metformin.93-95 In one 4-year, randomized, double-blind study, the addition of dapagliflozin provided greater glycemic durability as well as sustained reductions in weight, systolic blood pressure, and hypoglycemia compared with glipizide.96 The rate of hypoglycemia was nearly 10-fold lower with dapagliflozin than with glipizide (5.4% vs. 51.5%). Urinary tract infections (UTIs) and genital mycotic infections are the most commonly reported adverse events associated with SGLT-2 inhibitors. A meta-analysis showed a 3-fold greater risk of genital mycotic infections in women and men with the addition of an SGLT-2 inhibitor to metformin than with metformin alone.98 In contrast, the meta-analysis found a similar rate of UTIs with the combination therapy vs metformin alone.

During the past year, the FDA has issued several drug safety communications regarding 1 or more SGLT-2 inhibitors. These are an increased risk for:

- bone fracture and decreased bone mineral density with canagliflozin97
- ketoacidosis and UTI with canagliflozin, dapagliflozin, and empagliflozin98
- acute kidney injury with canagliflozin and dapagliflozin99
- leg and foot amputations, mostly affecting the toes, with canagliflozin.100

A small, dose-dependent increase in low-density lipoprotein cholesterol is seen when an SGLT-2 inhibitor is added to metformin.84,85,87 In the CV outcome study in patients at high CV risk, the SGLT-2 inhibitor empagliflozin showed a significant reduction in composite MACE outcome (14% relative risk reduction) as well as all-cause mortality (32% relative risk reduction).101

BASAL INSULIN

Basal insulin is another recommended option across the spectrum of T2DM management, including as add-on therapy to lifestyle management and metformin. Basal insulin should be considered a part of any combination regimen when hyperglycemia is severe, especially if the patient is symptomatic or if catabolic features, eg, weight loss or ketosis, are evident.2 Basal insulin has the advantage of effectively lowering blood glucose when other medications may not. On the other hand, hypoglycemia and weight gain serve as barriers to treatment with basal insulin.49,102,103

ESCALATION FROM SINGLE-AGENT TO TRIPLE-AGENT THERAPY

Treatment of patients with T2DM has generally involved the sequential addition and titration of therapy until the glycemic targets are achieved.2 The concept of intensifying metformin monotherapy by adding 2 medications at the same time, as well as combining therapy for initial treatment of diabetes, has been proposed to help patients achieve glycemic control earlier in the disease course. Four clinical trials investigated the simultaneous addition of 2 medications with complementary mechanisms of action in patients who had not achieved their glycemic target despite maximal doses of metformin. These 4 trials include the simultaneous addition to metformin of exenatide and dapagliflozin, saxagliptin and dapagliflozin, alogliptin and pioglitazone, and empagliflozin and linagliptin.96,104-106 In patients with mean HbA1c of 7.9% to 9.3% at baseline, these 24- to 52-week trials showed greater HbA1c reduction with the simultaneous addition of the 2 medications vs single-agent therapy.89,104-106 Combination therapy after metformin may decrease the risk of therapeutic inertia and initially yields better HbA1c control, but whether this approach leads to longer-term benefit remains to be proven.

SUMMARY

Several classes of antihyperglycemic medications have been recommended in guidelines by both the ADA/EASD and AACE/ACE for patients who have not achieved adequate glycemic control with metformin and lifestyle management alone. Important attributes for second-line therapy include clinically meaningful glycemic efficacy, weight loss instead of weight gain, low risk of hypoglycemia, favorable cost, and tolerable side effect and adverse event profiles. SGLT-2 inhibitors and GLP-1RAs both have good glycemic efficacy, weight loss, low risk of hypoglycemia when not combined with agents known to cause hypoglycemia, and good glycemic durability. In addition, empagliflozin and lixivatide have demonstrated a favorable effect on MACE in high-risk individuals. SGLT-2 inhibitors and GLP-1RAs have a well-defined
side effect profile, primarily involving an increase in myocytic infections and UTIs for SGLT-2 inhibitors and GI side effects that diminish over time for GLP-1RAs. DPP-4 inhibitors have lower glycemic efficacy and are not associated with weight loss, although they are well tolerated and have few associated side effects or adverse events. TZDs have very good glycemic efficacy and a low incidence of hypoglycemia, but are associated with weight gain and side effects that include peripheral edema, increased risk for exacerbation of heart failure, and fracture. SUs have good glycemic efficacy and low cost, but have a high incidence of hypoglycemia and weight gain. Basal insulin also has good glycemic efficacy, but has a high incidence of hypoglycemia and weight gain. Recognizing the benefits and limitations of each class of medication and considering the differences among medications in light of specific patient needs and preferences will help clinicians individualize treatment and improve patient outcomes.

REFERENCES

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Community-Acquired Bacterial Pneumonia: Is There Anything New?

Hans Liu, MD, FACP

INTRODUCTION
The management of patients with community-acquired pneumonia (CAP) is an ongoing challenge in the primary care setting. This is due, in part, to the fact that management guidelines in the United States were published nearly a decade ago. Furthermore, there has been a dearth of new treatments. But that may be about to change. Management guidelines are being updated by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) and are expected to be released this summer. In addition, several new antibiotics for the treatment of CAP are on the horizon.

EPIDEMIOLOGY
Streptococcus pneumoniae has been considered the leading bacterial cause of CAP. However, recent studies have shown variability in how often S pneumoniae is isolated from patients with pneumonia. The introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in 2000 for children, and the 13-valent pneumococcal conjugate vaccine (PCV13) in 2010 for children, immunocompromised adults, and adults ages 65 years or older has had a significant impact on the incidence of related infections. One multicenter study showed a 16% to 32% decrease in cases of CAP in children and infants following introduction of PCV13. Invasive pneumococcal disease rates have also decreased among unvaccinated older children, adults, and the elderly—particularly contacts of vaccine recipients, suggesting herd immunity protective effects.

However, CAP continues to be a concern, particularly among older adults, with an estimated 950,000 cases per year in adults younger than 65 years and 1.3 million cases per year in adults 65 years or older. Pneumonia is currently the leading cause of infection-related death and, combined with influenza, is the 8th leading cause of death in the United States. Furthermore, individuals with CAP have a greater 10-year mortality compared with controls (hazard ratio, 1.65; average age 59 years in a case-control study).

Morbidity in the adult population is associated with significant duration of illness (average 31.8 days and 10.2 days per inpatient episode and outpatient episode, respectively), and overall health care cost (approximately $11,000 to $51,000 and $1,000 to $5,600 per inpatient episode and outpatient episode, respectively). CAP in adults ages 50 years or older is also associated with significant absenteeism and decreased work productivity. Primary care physicians carry much of the burden of CAP diagnosis and treatment because approximately 72% of CAP episodes are managed on an outpatient basis.

ETIOLOGY AND PATHOGEN SUSCEPTIBILITY
Among the challenges of outpatient management of CAP is the lack of a confirmed etiologic diagnosis to guide initial treatment. Even with the use of current laboratory diagnostic testing, no pathogen was detected in 62% of 2259 hospitalized patients with radiographic evidence of CAP in a surveillance study in 5 US hospitals. Another recent study of patients hospitalized with CAP (N=323) in the United Kingdom reported a much higher detection rate, identifying a pathogen in 87%. While reasons for the difference in the detection rates between the 2 studies are not clear, possible reasons for the low detection rate include an inability to obtain a good diagnostic specimen, insensitive diagnostic tests for known pathogens, or lack of available rapid testing for some viruses and other respiratory pathogens.

A key management challenge is the wide variety of potential pathogens and variability from site to site, as well as the impact of antibiotic use on pathogen detection. Among causative pathogens for CAP identified in the US study, human rhinovirus was the most common, followed by influenza A or B. Streptococcus pneumoniae remained the leading bacterial cause of CAP, accounting for 5% of all pathogens detected and 37.6% with an identified bacterial
pathogen. In the UK study, Haemophilus influenzae and S pneumoniae were the most common bacteria identified, detected in 40% and 36% of patients with CAP, respectively. Rhinovirus was the most common virus identified; it was detected in 13% of patients with CAP. Other bacterial causes of CAP include Moraxella catarrhalis, Staphylococcus aureus (typically occurring after influenza infection, and increasingly involving methicillin-resistant S aureus [MRSA]), and Group A streptococci, as well as the “atypical” bacterial pathogens: Chlamydophila pneumoniae, Mycoplasma pneumoniae, and Legionella species. Improvements in diagnostic techniques allowing for better identification of viruses and fastidious bacteria have resulted in a smaller percentage of CAP cases now being attributed to typical bacterial pathogens.

The percentage of outpatients with S pneumoniae identified as the pathogen is higher than in inpatients. A meta-analysis of 46 studies published from 1990 through 2007 indicates that S pneumoniae was the pathogen in 38% of outpatients in Europe. Another multinational study conducted from 2013 to 2014 involving 860 patients (mostly outpatients) with CAP showed that S pneumoniae was the causative pathogen in 24%.

Another challenge to CAP management is the increasing incidence of antibiotic resistance among common bacterial pathogens. Between 2010 and 2014, S pneumoniae resistance rates increased markedly for penicillin and macrolides; somewhat less so for amoxicillin-clavulanate, tetracycline, and trimethoprim-sulfamethoxazole; and negligibly for the fluoroquinolone levofloxacin (FIGURE). S pneumoniae resistance to macrolides is widespread and concentrated particularly along the East Coast and the Southwest parts of the United States, with rates up to 60%. This is of particular concern because macrolides are considered a first-line empiric treatment for CAP.

Ceftriaxone, another antibacterial agent commonly used in the hospital and emergency department for bacterial CAP, also has been subject to some reduction in activity against S pneumoniae, with susceptibility rates decreasing from 97.4% to 87.5% between 1998 and 2009. Mycoplasma pneumoniae, which typically produces a mild “walking” pneumonia, has demonstrated increasing resistance to macrolide antibiotics (likely associated with the widespread use of azithromycin), with wide geographic variability, ranging from 7% in Seattle to 50% in New Jersey.

Because the epidemiology of pathogens and resistance patterns are associated with large geographical variations, knowledge of local etiology and susceptibility patterns is crucial for the appropriate choice of empiric antimicrobial treatment for CAP. Primary care physicians can consult with their local public health department or local infectious disease specialist to determine resistance patterns in their communities.

**DEFINITION**

The common role of viruses and bacteria and less-common role of fungi in the etiology of CAP has contributed to difficulties in diagnosis and treatment, and underscores the importance of differentiating among the types of pathogens. In 2014, the US Food and Drug Administration (FDA) developed a definition of community-acquired bacterial pneumonia (CABP) to be applied to clinical studies in the development of drugs to treat CABP.

CABP is an acute bacterial infection of the pulmonary parenchyma that is:

- associated with chest pain, cough, sputum production, difficulty breathing, chills, rigors, fever, or hypotension, and is
- accompanied by the presence of a new lobar or multilobar infiltrate on a chest radiograph.

**RISK STRATIFICATION AND DIAGNOSTICS**

Possibly the most important clinical decision made by the physician in the management of patients with CAP is
whether to treat as an inpatient or outpatient, as this has a direct impact on the intensity of laboratory evaluation, location and type of antibiotic therapy, and costs. Two instruments that help guide this decision utilize risk factors to predict mortality risk; the Pneumonia Severity Index (PSI), also called the Pneumonia Patient Outcomes Research Team (PORT) Severity Index, is used in the United States, and the CURB-65 (Confusion, Urea nitrogen, Respiratory rate, Blood pressure, 65 years of age and older) pneumonia severity score is more commonly used in the United Kingdom and Asia (TABLE 1). The PSI puts patients in risk classes (I-V) based on age, comorbidities (neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, or renal disease), vital signs, mental status, gender, nursing home residence, and laboratory and radiographic findings. The CURB-65 score assigns points for confusion, blood urea >19 mg/dL, respiratory rate ≥30 min, blood pressure <90 mm Hg (systolic) or ≤60 mm Hg (diastolic), and age ≥65 years.

<table>
<thead>
<tr>
<th>PSI risk class*</th>
<th>No. of points</th>
<th>Mortality (%)</th>
<th>Recommended site of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>——</td>
<td>0.1</td>
<td>Outpatient</td>
</tr>
<tr>
<td>II</td>
<td>≤70</td>
<td>0.6</td>
<td>Outpatient</td>
</tr>
<tr>
<td>III</td>
<td>71-90</td>
<td>2.8</td>
<td>Outpatient or brief inpatient</td>
</tr>
<tr>
<td>IV</td>
<td>91-130</td>
<td>8.2</td>
<td>Inpatient</td>
</tr>
<tr>
<td>V</td>
<td>&gt;130</td>
<td>29.2</td>
<td>Inpatient; consider ICU</td>
</tr>
</tbody>
</table>

CURB-65 Score†
- 0 or 1 <3 Likely suitable for home treatment
- 2 9 Consider hospital-supervised treatmentb
- 3-5 15-40 Inpatientc

Abbreviations: CURB, confusion, urea nitrogen, respiratory rate, blood pressure, 65 years of age and older; ICU, intensive care unit; PSI, Pneumonia Severity Index.

*Absence of risk factors.
†Options may include short inpatient stay or hospital-supervised outpatient.

The empirical outpatient management of the majority of patients with CAP has been hindered by the delay in, and the accuracy of, diagnosis associated with culture-based methods. Polymerase chain reaction (PCR) analysis has emerged as a more rapid diagnostic technique that provides a result within 1 day. PCR testing has improved pathogen detection over culture-based methods (87% vs 39% in a study of 323 patients) and is less likely to be negatively affected by antibiotic administration prior to sampling. While PCR testing helps differentiate viral from bacterial etiology, insurance coverage may not pay for the cost and patients might not wish to wait the short time needed for the result. Moreover, waiting for PCR test results would not be appropriate if a patient’s clinical presentation already warranted hospital admission. Urinary antigen testing for Legionella pneumophila and S pneumoniae is a consideration in critically ill patients with CAP.

Urinary antigen testing, notably for S pneumoniae and Legionella species, is readily accessible and provides rapid turnaround time (about 1 day) and reasonable sensitivity and good specificity. However, current guidelines do not provide clear recommendations regarding appropriate situations in which testing should be performed. Urinary antigen testing is often used by emergency medicine and other admitting providers. Although I have not had good experience with either urinary antigen test in patients with CAP, it is another way of looking for an etiologic diagnosis in patients with CAP who have already received antibiotics.

**CURRENT OUTPATIENT TREATMENT OF CAP**

The 2007 IDSA/ATS guidelines recommend broad-spectrum coverage for many patients with CABP, including those with...
Collateral damage may also encompass other unintended, serious consequences of antibiotic therapy. For example, the FDA recently strengthened warnings regarding the serious risks for tendinopathy, peripheral neuropathy, and central nervous system effects associated with fluoroquinolones.40,41

Approximately 3 years ago, the FDA strengthened warnings regarding the risk of QT interval prolongation and torsades de pointes with the macrolide azithromycin.42 The possibility of collateral damage and other adverse events are considerations in treatment selection.

“STATE OF THE ART”
IN CABP/CAP MANAGEMENT

In light of current information on epidemiology, antibiotic resistance patterns, risk factors for poor outcomes, and available diagnostic tools and antibiotics, the following is a “state-of-the-art” approach I recommend for the management of CAP:

1. Make a preliminary diagnosis based on symptomatic presentation.
2. Consider risk factors for poor outcomes, eg, older age, chronic obstructive pulmonary disease, heart failure, smoking.
3. Consider acquiring specimens for laboratory analysis (complete blood count and metabolic panel, chest x-ray, sputum or other cultures) if:
   a. on first visit, patient presents in poor health or with risk factors for poor outcomes, or
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   b. For a relatively healthy adult with cough and chest discomfort that may indicate viral pneumonia or atypical respiratory infection (usually mycoplasma), consider a macrolide or doxycycline.
   c. If a bacterial pathogen is suspected or the patient is ill or at risk for poor outcome AND considering local resistance patterns:
      i. consider a macrolide or doxycycline for narrow coverage
      ii. consider amoxicillin-clavulanate or trimethoprim-sulfamethoxazole for broader coverage, or
      iii. consider fluoroquinolone or a macrolide + β-lactam for broad-spectrum coverage.

COLLATERAL DAMAGE

Another challenge in CAP treatment is managing collateral damage. This term typically refers to the ecological adverse effects of antibiotic therapy, ie, the selection of drug-resistant organisms and the unwanted development of colonization or infection with multidrug-resistant organisms (eg, *Clostridium difficile* colitis or antibiotic-associated diarrhea).29

Comorbidities or other risks for drug-resistant *S pneumoniae*. Although the 2007 IDSA/ATS guidelines recommend specific classes of antibacterial agents for empiric therapy, subsequent studies and meta-analyses have failed to demonstrate a clearly superior regimen among various monotherapy and combination therapy regimens.28-35

It is noteworthy that, despite a significant increase in macrolide resistance in some regions, which was a concern at the time the IDSA/ATS guidelines were developed, macrolides still play an important role in CAP therapy (in part because of their coverage of atypical respiratory pathogens).13 This underscores the importance of determining local resistance patterns to guide treatment, particularly empiric treatment. Doxycycline may be an appropriate alternative for patients with mild symptoms and a high likelihood of an atypical pathogen, but many clinicians feel it is not sufficient for very ill patients due to increasing resistance in key bacterial pathogens.36

The use of oxygen saturation in managing patients with CAP in the outpatient setting is not well studied, although some evidence suggests that oxygen saturation <92% is associated with major adverse events.37 However, outpatients with CAP in the outpatient setting is not well studied, although some evidence suggests that oxygen saturation <92% is associated with major adverse events.37 However, outpatients with CAP who have a low oxygen saturation, regardless of the cause, understandably may need more intensive management.

Nonresponsiveness to treatment is yet another challenge in the empiric management of patients with CAP in the primary care setting. In a 2016 retrospective analysis of 250 adults with CAP (the majority of whom had chest x-rays) who were originally diagnosed in an outpatient facility by a primary care provider, 34% were considered nonresponsive to empiric therapy, ie, they failed to respond to antibiotic therapy. This resulted in worsening symptoms or delayed achievement of clinical stability.38 Predictors of nonresponse were being a former smoker (odds ratio [OR], 2.27; *P*<.01), initial presentation to urgent care (OR, 2.10; *P*=.02), and myalgia (OR, 2.79; *P*=.003). Given the frequent association of myalgia with influenza, it is possible that the study population included a large proportion of patients with primary viral pneumonia expected to be unresponsive to antibacterial therapy.38 However, lack of response to treatment makes it difficult for the health care provider to decide about maintaining, changing, or discontinuing current therapy.

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NEW ANTIBIOTICS FOR CABP ON THE HORIZON

Only 2 new antibiotics have become available in the United States for the treatment of bacterial pneumonia since the publication of the 2007 IDSA/ATS guidelines. One is tigecycline, the first drug in the glycylcycline class of antibiotics, and the other is ceftaroline fosamil, a broad-spectrum cephalosporin. Both are administered parenterally and are expensive, with limited potential for the treatment of patients with CABP who do not require prolonged hospitalization.

There are several antibiotics in late-stage development for the treatment of patients with CABP (TABLE 2). Omadacycline is an oral and intravenous tetracycline with potent activity comparable to tigecycline against resistant Gram-positive bacteria, including *S pneumoniae* and MRSA. Omadacycline has good oral bioavailability and is not associated with significant nausea or vomiting.

Lefamulin is an oral and intravenous pleuromutilin antibiotic with potent activity against multidrug-resistant strains of *S pneumoniae* and macrolide-sensitive and macrolide-resistant *M pneumoniae*. Lefamulin has been granted qualified infectious disease product/fast-track status by the FDA, and patients with moderate/severe CABP are being enrolled in phase 3 Lefamulin Evaluation Against Pneumonia-1 (LEAP-1) and LEAP-2 trials comparing lefamulin with moxifloxacin with or without linezolid [NCT02559310 and NCT02813694].

Solithromycin is an oral and intravenous 4th-generation macrolide that is highly active against macrolide-resistant *S pneumoniae*, *M catarrhalis*, and *Mycoplasma pneumoniae*. Solithromycin is less active (1 tube dilution) than azithromycin against *H influenzae*, but has good activity against *S aureus*, including MRSA. In patients with moderate/moderately severe CABP, solithromycin demonstrated noninferiority vs levofloxacin and moxifloxacin in achieving symptom response at 72 hours.

**IMPLICATIONS FOR PRIMARY CARE PRACTICE**

CAP remains a significant cause of morbidity and mortality in the United States, incurring a high use of healthcare resources. In the current era of cost containment, standards-driven care, and concerns about antibiotic resistance, there is great interest in using targeted-spectrum therapy, balancing the risks of therapy (including adverse events) with likelihood of success, and avoiding relapse and hospitalization.

Advances in diagnostic testing have led to a new appreciation of a wider array of pathogens involved in CAP—notably viruses, some of which are treatable (eg, influenza). Pathogen susceptibility is changing (eg, *S pneumoniae*, mycoplasmal), requiring physicians to remain up to date on local resistance patterns to guide empiric treatment. Additionally, after a dearth of new antibiotics over the last decade for CABP, several are on the horizon.

**REFERENCES**


**TABLE 2  Antibiotics on the horizon for community-acquired bacterial pneumonia**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Omadacycline</th>
<th>Lefamulin</th>
<th>Solithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
<td>Tetracycline</td>
<td>Pleuromutilin</td>
<td>4th-generation macrolide</td>
</tr>
<tr>
<td><strong>Stage of development</strong></td>
<td>Early phase 3</td>
<td>Early phase 3</td>
<td>FDA issued complete response letter in December 2016 requiring further safety investigations.</td>
</tr>
<tr>
<td><strong>Pathogens covered</strong></td>
<td>Resistant Gram-positive bacteria, including <em>S pneumoniae</em> and MRSA</td>
<td>Multi-drug-resistant strains of <em>S pneumoniae</em>, macrolide-sensitive and macrolide-resistant <em>M pneumoniae</em></td>
<td>Macrolide-resistant <em>S pneumoniae</em> and <em>M pneumoniae</em>, <em>M catarrhalis</em>; good activity against <em>S aureus</em>, including community-acquired MRSA</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Oral and IV</td>
<td>Oral and IV</td>
<td>Oral and IV</td>
</tr>
</tbody>
</table>

**Abbreviations:** FDA, US Food and Drug Administration; IV, intravenous; MRSA, *Methicillin-resistant Staphylococcus aureus*; PDUFA, Prescription Drug User Fee Act; *S aureus*, *Staphylococcus aureus*; *S pneumoniae*, *Streptococcus pneumoniae*.
28. Nie W, Li B, Xiu Q. ßeta-lactam/macrolide dual therapy versus ß-lactam mono-
26. Couturier MR, Graf EH, Griffin AT. Urine antigen tests for the diagnosis of respiratory
23. Lim WS, Baudouin SV, George RC, et al; Pneumonia Guidelines Committee of
18. Viasus D, Garcia-Vidal C, Carratalà J. Advances in antibiotic therapy for community-
14. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-ac-
11. Jain S, Self WH, Wunderink RG, et al; CDC Epic Study Team. Community-ac -
2009;64(suppl 3):iii1-iii55.
2016;16(4):421-430.
2016;16(4):241-430.
2009;21(0):1470-1472.
2013;64(suppl 3):iii1-iii55.
2011;23(1):554.
2015;46(3):3662-3668.
2016;16(4):421-430.
2015;21(8):1470-1472.
2013;64(suppl 3):iii1-iii55.
2016;16(4):421-430.
2016;16(4):421-430.
2009;21(0):1470-1472.
2016;51(5):541-548.
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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is an independent risk factor for cardiovascular disease, conferring about a twofold greater risk for a wide range of cardiovascular diseases. Cardiovascular disease is the leading cause of death among individuals with T2DM. Besides vascular events, which include myocardial infarction and stroke, patients with diabetes are at a high risk for developing heart failure and heart failure-related death, with a 15% increase in the risk of heart failure for every 1% increase in glycated hemoglobin (HbA1c) above 7.5%. While several studies have shown an association between HbA1c lowering and a reduction in microvascular adverse events, including retinopathy and nephropathy, consistent results have not been seen between blood glucose control and either macrovascular disease risk or cardiovascular mortality.

The potential cardiovascular benefits gained by lowering HbA1c were further tempered by a 2007 meta-analysis of rosiglitazone conducted by Nissen et al. This meta-analysis of 42 clinical trials found an elevated risk for myocardial infarction with an odds ratio of 1.43 (95% confidence interval [CI], 1.03-1.98; \( P = .03 \)) for rosiglitazone relative to the control group. The odds ratio for cardiovascular death was also elevated at 1.64 (95% CI, 0.98-2.74), although this did not reach statistical significance (\( P = .06 \)). The results of this meta-analysis added to concerns from other trials regarding an increased risk of myocardial infarction with pioglitazone and rosiglitazone. Although an increased risk of myocardial infarction with rosiglitazone was not corroborated in the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes) trial, the US Food and Drug Administration (FDA) issued a safety alert warning of the risk of myocardial infarction and cardiovascular death with rosiglitazone. As a consequence, rather than targeting the potential for cardiovascular benefit, these data and the resulting FDA action led to a focus on the cardiovascular safety of antihyperglycemic medications. That impacted the subsequent design and conduct of clinical trials in patients with diabetes mellitus.

FDA CARDIOVASCULAR RISK GUIDANCE

In 2008, the FDA took additional action related to cardiovascular safety of medications for treating T2DM by issuing the industry guidance Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. This guidance provided recommendations about how industry sponsors should demonstrate that a new antihyperglycemic agent to treat T2DM is not associated with an unacceptable increase in cardiovascular risk.

For new clinical trials, the guidance recommended the establishment of an independent cardiovascular endpoints committee to prospectively adjudicate cardiovascular events during phase 2 and 3 trials. The events to be assessed included major adverse cardiovascular events (MACE), among them cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The clinical trials should be designed so that a meta-analysis could be performed that accounts for important study design features and explores similarities and/or differences in patient subgroups, eg, age, sex, and race. A protocol describing the statistical methods and endpoints for the meta-analysis also needs to be provided.

For the statistical comparison, the incidence of important cardiovascular events with the new antihyperglycemic medication is to be compared with a control group. If the upper limit of the two-sided 95% CI for the estimated risk ratio is less...
than 1.8, a determination of noninferiority can be made on an interim basis. Otherwise, an additional single, large safety trial should be conducted that alone, or added to other trials, would be able to satisfy the 1.8 upper limit. If the upper limit for the estimated risk ratio is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval, a postmarketing trial is generally needed to definitively show that the upper limit of the two-sided 95% CI for the estimated risk ratio is less than 1.3.11

**TRADITIONAL CLINICAL OUTCOMES TRIALS VS DIABETES MEDICATION SAFETY TRIALS**

The cardiovascular clinical trials of antihyperglycemic medications required by the 2008 FDA guidance are different from the traditional clinical trials that have been conducted to assess cardiovascular risk. In traditional clinical trials, the general goal is to establish that the cardiovascular risk of an active treatment is lower than the risk observed with a comparator (placebo or another active medication). That is, the trials need to demonstrate that the cardiovascular benefits of one treatment are superior to another.

In contrast, for trials of antihyperglycemic medications required by FDA, the goal is to demonstrate that the new antihyperglycemic medication is not associated with an unacceptable increase in cardiovascular risk compared with placebo as part of standard care in patients with T2DM. That is, the cardiovascular safety of the new antihyperglycemic medication is noninferior (ie, similar) to placebo as part of standard care. If noninferiority is demonstrated, the possible superiority of the new antihyperglycemic medication can then be assessed as well, but the primary aim is to prove safety. As noted earlier, major adverse cardiovascular events are the focus, although other endpoints that might be investigated include hospitalization for acute coronary syndrome, urgent revascularization, unstable angina, and heart failure.11

Patients in the diabetes medication safety trials are generally at higher cardiovascular risk since they are more likely to show benefit or harm over a short period of time. This heightened risk allows for rapid assessment of cardiovascular safety, and with logistically feasible follow-up, provides insights into longer-term cardiovascular risks or benefits.12

**RECENT CARDIOVASCULAR SAFETY TRIALS WITH ANTIHYPERGLYCEMIC MEDICATIONS**

Sixteen large, randomized, double-blind, parallel, placebo-controlled, multicenter trials involving 145,000 participants have been initiated in accordance with the FDA guidance.13-19 Thus, all 7 trials involving 3 different classes of medication, ie, dipeptidyl peptidase-4 inhibitor (DPP-4i), glucagon-like peptide-1 receptor agonist (GLP-1RA), and sodium glucose cotransporter-2 inhibitor (SGLT-2i), have excluded an unacceptable level of cardiovascular risk as described in the 2008 FDA guidance.

While the demonstration of noninferiority for the primary composite endpoint in all 7 trials is reassuring regarding the cardiovascular safety of these 3 classes of medications, other data raised concerns regarding the DPP-4i class. Among these, the HRs for heart failure hospitalization varied among the DPP-4i class drugs, ranging from 1.00 for sitagliptin to 1.27 for saxagliptin, raising a potential concern for saxagliptin and a less-evident trend for alogliptin. It was, however, not entirely clear if saxagliptin and alogliptin actually increased the risk of heart failure hospitalization because the trials conducted under the 2008 FDA guidance had limited data collection for accurately assessing heart failure.12

Since then, a retrospective, observational study of an insurance claims database demonstrated no association between heart failure hospitalization or several other cardiovascular outcomes and treatment with a DPP-4i agent relative to sulfonylurea therapy or treatment with saxagliptin relative to sitagliptin.20 Nonetheless, these findings in the cardiovascular trials led the FDA to include a heart failure warning in the prescribing information for saxagliptin and alogliptin.21,22

While the focus of clinical trials required by the 2008 FDA guidance was safety, the HRs of the composite MACE primary endpoints observed in the empagliflozin, liraglutide, and semaglutide (investigational) trials demonstrated noninferiority; they also demonstrated superiority, each with an upper limit of the 95% CI less than 1.16,18,19 For both empagliflozin and liraglutide, significant benefit was observed primarily for cardiovascular death, whereas the benefit with semaglutide was driven primarily by a reduction in nonfatal stroke.16,18,19 Differences in the magnitude of the beneficial effects observed in these trials are likely related to differences
### TABLE 1 | Cardiovascular outcome trials for new antihyperglycemic medications in type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Medication</th>
<th>NCT #</th>
<th>Trial</th>
<th>Population</th>
<th>Estimated enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SGLT-2 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>01032629</td>
<td>CANVAS</td>
<td>M/F age ≥30 y w/CVD or age ≥50 y with high CV risk</td>
<td>4331</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>01989754</td>
<td>CANVAS-R</td>
<td>M/F age ≥30 y w/CVD or age ≥50 y with high CV risk</td>
<td>5813</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>02065791</td>
<td>CREDENCE</td>
<td>M/F age ≥30 y w/UACR &gt;300 and ≤5000 mg/g</td>
<td>4200</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>01730534</td>
<td>DECLARE-TIMI 58</td>
<td>M/F age ≥40 y with high CVD risk</td>
<td>17,276</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>01131676</td>
<td>EMPA-REG OUTCOME</td>
<td>M/F age ≥18 y with established CVD</td>
<td>7064</td>
</tr>
<tr>
<td>Ertugliflozin*</td>
<td>01986881</td>
<td>VERTIS CV</td>
<td>M/F age ≥40 y w/coronary artery disease, cerebrovascular disease, and/or peripheral artery disease</td>
<td>8000</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alogliptin</td>
<td>00968708</td>
<td>EXAMINE</td>
<td>M/F age ≥18 y diagnosed with ACS within 15-90 days</td>
<td>5380</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>01897532</td>
<td>CARMELINA</td>
<td>M/F age ≥18 y w/high-risk albuminuria and previous macrovascular disease and/or impaired renal function</td>
<td>8300</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>01243424</td>
<td>CAROLINA</td>
<td>M/F age 40-85 y w/pre-existing CVD or specified diabetes EOD or age ≥70 y or ≥2 CV risk factors</td>
<td>6115</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>01107886</td>
<td>SAVOR-TIMI53</td>
<td>M/F age ≥40 y with established CVD and/or multiple risk factors</td>
<td>18,206</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>00790205</td>
<td>TECOS</td>
<td>M/F age ≥50 y with pre-existing CVD</td>
<td>14,671</td>
</tr>
<tr>
<td><strong>GLP-1 receptor agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albiglutide</td>
<td>02465515</td>
<td>HARMONY</td>
<td>M/F age ≥40 y w/coronary artery disease, cerebrovascular disease, and/or peripheral artery disease</td>
<td>9400</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>01394952</td>
<td>REWIND</td>
<td>M/F age ≥50 y w/established vascular disease or age ≥55 y w/subclinical vascular disease or age ≥60 y w/2 CV risk factors</td>
<td>9622</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>01144338</td>
<td>EXSCEL</td>
<td>M/F age ≥18 y</td>
<td>14,000</td>
</tr>
<tr>
<td>Exenatide in EUROS*</td>
<td>01455896</td>
<td>ITCA 650</td>
<td>M/F age ≥40 y with history of coronary, cerebrovascular, or peripheral artery disease</td>
<td>4000</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>01179048</td>
<td>LEADER</td>
<td>M/F age ≥50 y w/CV, cerebrovascular, or peripheral vascular disease or chronic renal failure or chronic heart failure or age ≥60 y with other specified risk factors of vascular disease</td>
<td>9340</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>01147250</td>
<td>ELIXA</td>
<td>M/F age ≥30 y w/ACS event leading to hospitalization</td>
<td>6076</td>
</tr>
<tr>
<td>Semaglutide*</td>
<td>01720446</td>
<td>SUSTAIN 6</td>
<td>M/F age ≥50 y w/CVD or age ≥60 y w/subclinical CVD</td>
<td>3297</td>
</tr>
</tbody>
</table>

**Note:** All trials are randomized, double-blind, parallel, placebo-controlled, and multi-center.

*Investigational in the United States.

**Abbreviations:** ACS, acute coronary syndrome (ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, or unstable angina); CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; EOD, end-organ damage; F, female; GLP-1, glucagon-like peptide-1; M, male; NCT, national clinical trial; SGLT-2, sodium-glucose cotransporter-2; UACR, urine albumin to creatinine ratio.

**Source:** ClinicalTrials.gov.
in patient population (primary or secondary prevention), study design, and duration of follow-up.

In these clinical trials, there were numerous exploratory analyses of the effects of these agents on other cardiovascular and renal endpoints. For empagliflozin, the risk of hospitalization for heart failure, cardiovascular and heart failure death, and nephropathy was significantly reduced. For liraglutide, the risk of microvascular events and nephropathy was significantly reduced. For semaglutide, the risks of nonfatal stroke, need for revascularization, and new or worsening nephropathy were significantly reduced, but the risk of retinopathy was increased. Although these trials suggest a potential benefit, they were not statistically powered or designed to evaluate these

### TABLE 2 Results of completed cardiovascular outcomes trials for antihyperglycemic medications in type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Trial</th>
<th>Medication</th>
<th>Primary endpoint</th>
<th>Heart failure hospitalization</th>
<th>All-cause death</th>
<th>Other key cardiovascular endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SGLT-2 inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>Empagliflozin</td>
<td>0.86e (0.74-0.99)</td>
<td>0.65 (0.50-0.85)</td>
<td>0.68 (0.57-0.82)</td>
<td>Silent myocardial infarction: 1.28 (0.70-2.33) Unstable angina hospitalization: 0.99 (0.74-1.34) Fatal or nonfatal stroke: 1.18 (0.89-1.56) Nonfatal stroke: 1.24 (0.92-1.67) Transient ischemic attack: 0.85 (0.51-1.42) Heart failure death</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVOR-TIMI53</td>
<td>Saxagliptin</td>
<td>1.00f (0.89-1.12)</td>
<td>1.27 (1.07-1.51)</td>
<td>1.11 (0.96-1.27)</td>
<td>Ischemic stroke: 1.11 (0.88-1.39) Unstable angina hospitalization: 1.19 (0.89-1.60) Doubling of creatinine, initiation of dialysis, renal transplantation, or creatinine &gt;6.0 mg/dL: 1.08 (0.88-1.32)</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>0.96g (upper-bound 1.16)</td>
<td>1.19 (0.90-1.58)</td>
<td>0.88 (0.71-1.09)</td>
<td>Nonfatal myocardial infarction: 1.08 (0.88-1.33) Nonfatal stroke: 0.91 (0.55-1.50)</td>
</tr>
<tr>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>0.98h (0.89-1.08)</td>
<td>1.00 (0.83-1.20)</td>
<td>1.01 (0.90-1.14)</td>
<td>Compositei: 0.99 (0.89-1.11)</td>
</tr>
<tr>
<td><strong>GLP-1 receptor agonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELIXA</td>
<td>Lixisenatide</td>
<td>1.02h (0.89-1.17)</td>
<td>0.96 (0.75-1.23)</td>
<td>0.94 (0.78-1.13)</td>
<td>Stroke: 1.12 (0.79-1.58) Unstable angina: 1.11 (0.47-2.62)</td>
</tr>
<tr>
<td>LEADER</td>
<td>Liraglutide</td>
<td>0.87h (0.78-0.97)</td>
<td>0.87 (0.73-1.05)</td>
<td>0.85 (0.74-0.97)</td>
<td>Composite: 0.88 (0.81-0.96) Retinopathy: 1.15 (0.87-1.52)</td>
</tr>
<tr>
<td>SUSTAIN 6</td>
<td>Semaglutide</td>
<td>0.74h (0.58-0.95)</td>
<td>1.11 (0.77-1.61)</td>
<td>1.05 (0.74-1.50)</td>
<td>Cardiovascular death: 0.98 (0.65-1.48) Unstable angina hospitalization: 0.82 (0.47-1.44) Retinopathy: 1.76 (1.11-2.78)</td>
</tr>
</tbody>
</table>

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2.

*Data are presented as hazard ratio (95% confidence interval).

*Composite of cardiovascular death, nonfatal myocardial infarction (excluding silent myocardial infarction), nonfatal stroke.

*Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke.

*Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke.

*Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina.

*Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization or hospitalization for unstable angina or heart failure.

*Investigational in the United States.
The unanimous findings of these 7 completed trials with respect to MACE have led some experts to recommend a reassessment of the 2008 FDA guidance. Experts also point out that a re-examination of the 2007 meta-analysis of rosiglitazone by Nissen et al, which provided the impetus for the 2008 FDA guidance, actually showed no imbalance in MACE events with rosiglitazone as the upper limit of the 95% CI for the HR was less than 1.30 (HR = 0.97; 95% CI, 0.79-1.18). Instead of requiring a phase 3 clinical trial to specifically assess cardiovascular risk, the experts opine that the information from the 7 completed and 9 ongoing trials should be integrated with other available evidence to inform a more targeted safety assessment strategy.

Moreover, this targeted strategy should be integrated with other FDA preapproval and post-marketing surveillance mechanisms.

**IMPLICATIONS FOR PRIMARY CARE**

The cardiovascular safety of antihyperglycemic medications came into question a decade ago, leading to the FDA action requiring that a phase 3 clinical trial be conducted to assess cardiovascular risk of the new antihyperglycemic medication relative to placebo as part of standard care. Of the 16 trials conducted under the 2008 FDA guidance, the 7 trials that have been completed show that the 3 different classes of medications do not pose an increased risk of MACE. These results should provide reassurance about cardiovascular risk with these medications. Moreover, the evidence

| TABLE 3 | Results of endpoints demonstrating cardiovascular benefit with empagliflozin, liraglutide, and semaglutide |
|---|---|---|
| Endpoint | Rate/100 patient-years | Hazard ratio (95% CI) |
| | Placebo | Study drug | |
| Empagliflozin | | |
| Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke | 4.39 | 3.74 | 0.86 (0.74-0.99) |
| All-cause death | 2.86 | 1.94 | 0.68 (0.57-0.82) |
| Cardiovascular death | 2.02 | 1.24 | 0.62 (0.49-0.77) |
| Heart failure hospitalization | 1.45 | 0.94 | 0.65 (0.50-0.85) |
| Heart failure hospitalization or cardiovascular death (excluding fatal stroke) | 3.01 | 1.97 | 0.66 (0.55-0.79) |
| Liraglutide | | |
| Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke | 3.9 | 3.4 | 0.87 (0.78-0.97) |
| Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina or heart failure | 6.0 | 5.3 | 0.88 (0.81-0.96) |
| All-cause death | 2.5 | 2.1 | 0.85 (0.74-0.97) |
| Cardiovascular death | 1.6 | 1.2 | 0.78 (0.66-0.93) |
| Microvascular event | 2.3 | 2.0 | 0.84 (0.73-0.97) |
| Nephropathy | 1.9 | 1.5 | 0.78 (0.67-0.92) |
| Semaglutide | | |
| Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke | 4.44 | 3.24 | 0.74 (0.58-0.95) |
| All-cause death, nonfatal myocardial infarction, nonfatal stroke | 4.81 | 3.66 | 0.77 (0.61-0.97) |
| Nonfatal stroke | 1.31 | 0.80 | 0.61 (0.38-0.99) |
| Revascularization | 3.85 | 2.50 | 0.65 (0.50-0.86) |
| New or worsening nephropathy | 3.06 | 1.86 | 0.64 (0.46-0.88) |

*Abbreviation: CI, confidence interval.
*Primary endpoint.*
regarding the cardiovascular benefits of empagliflozin, liraglutide, and semaglutide is especially encouraging.

**ONGOING DIABETES MEDICATION OUTCOME TRIALS**

The ongoing diabetes medication outcome trials will provide additional data concerning the cardiovascular safety of the remaining DPP-4i, GLP-1RA, and SGLT-2i agents. These trials will include data from adults with kidney disease and other diabetes-related end organ damage. Due to the large numbers of patients in these trials relative to phase 3 safety and efficacy trials conducted for regulatory approval, these outcome trials will provide the opportunity to learn more about rare adverse events, as well as potential differences among the medications.

**REFERENCES**

Advances in medicine have contributed to improved health and increased longevity, but the rising cost of health care has strained both governmental and individual budgets. Patient access to health care services also has been affected, leading to the implementation of numerous strategies to manage these rising costs. The Hatch-Waxman Act of 1984 led to the availability of generic versions of branded drugs, with an estimated $1.7 trillion in savings from 2005 to 2014. More recently, in 2010 the US Congress enacted the Patient Protection and Affordable Care Act (PPACA) that included provisions to improve access to biologic therapies. Specifically, the PPACA introduced the 351(k) pathway to define the requirements needed for submission of a Biologic License Application (BLA) for approval of biosimilar products that are highly similar to their reference product. This article introduces key issues in the evolving US landscape of follow-on biologics, a category of biological products that includes biosimilars, and the implications for the primary care provider. To facilitate understanding, a glossary of terms is provided in Table 1.

FOLLOW-ON BIOLOGICS VS BIOSIMILARS

Sponsors of follow-on biologics can submit their applications for approval by the US Food and Drug Administration (FDA) under 2 distinct pathways. Prior to 2010, the reference biologic products for insulin, human growth hormone, and calcitonin were submitted as New Drug Applications (NDAs); in contrast, most other biologic products filed their original submissions as BLAs. Under the FDA framework, follow-on biologics use the same approval pathway as was used by their reference product; consequently, follow-on biologics for insulin, human growth hormone, and calcitonin are filed as NDAs. On March 23, 2020, pursuant to the PPACA, the dual submission pathways for follow-on biologics will come to an end. After this date, all follow-ons will submit using a BLA and all follow-on biologics previously submitted using an NDA will be deemed to be biosimilar. While the FDA has not yet defined these transition rules, it is reasonable to assume that a follow-on biologic previously approved as an NDA and otherwise meeting the scientific and legal requirements of a biosimilar will no longer be referred to as a...
A follow-on biologic and will be referred to as a biosimilar as of March 2020.7

An abbreviated regulatory process for approval allows a follow-on biologic to rely upon data that the follow-on sponsor did not generate, such as published literature or previous findings of safety and efficacy for a reference biomedicine product.5,14 Whereas the development of a new drug or biologic requires extensive clinical testing, follow-on biologics may use an abbreviated development program as outlined by the PPACA and FDA guidance (FIGURE 2).5 These applications will include preclinical assessment along with phase 1 and phase 3 clinical studies. Phase 2 studies are not required to establish similarity to the reference drug. Phase 1 studies are conducted in a small number of subjects to demonstrate that the follow-on biologic has similar pharmacokinetic and pharmacodynamic properties to its reference product. Phase 3 studies are larger studies designed to confirm efficacy and safety, including the immunogenicity profile. To be approved as a follow-on biologic, there must be no clinically meaningful differences between the follow-on biologic and the reference product. Five biosimilars have been approved by the FDA through the BLA pathway since 2015 (TABLE 2).

In December 2015, the FDA approved Basaglar (insulin glargine) as a follow-on biologic to Lantus. Basaglar was

![FIGURE 1](link)

**FIGURE 1** Development pathways for follow-on biologics

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved product</td>
<td>Listed drug relied upon if approved under the 505(b)(1) pathway; reference product if approved under a biologics license application (BLA)</td>
</tr>
<tr>
<td>Biosimilar</td>
<td>A biological product shown to be highly similar to the reference product, notwithstanding minor differences in clinically active components and with no clinically meaningful differences compared with the reference product in terms of safety, purity, and potency</td>
</tr>
<tr>
<td>Follow-on biologic</td>
<td>A biologic product shown to be safe and effective compared with the listed drug relied upon where some of the supporting evidence comes from studies not conducted by/for the sponsor and for which the sponsor has not obtained a right of reference</td>
</tr>
<tr>
<td>Generic drug</td>
<td>A drug that is chemically identical to a branded drug</td>
</tr>
<tr>
<td>Interchangeable</td>
<td>A biosimilar supported by evidence that it can be expected to produce the same clinical result as the reference product in a patient and, if administered more than once, the risk in terms of safety or diminished efficacy of alternating or switching between the biosimilar and reference product is not greater than the risk of using the reference product without such alternation or switch</td>
</tr>
<tr>
<td>Reference biologic product</td>
<td>The single biological product licensed under section 351(a) of the Public Health Service Act against which a biological product is evaluated in a 351(k) application</td>
</tr>
<tr>
<td>Substitution</td>
<td>The practice of substitution occurs at the pharmacy and is regulated by state laws</td>
</tr>
</tbody>
</table>

**TABLE 1** Glossary of terms5,12-14

The first follow-on insulin approved in the United States, and was submitted, like Lantus, using an NDA. More biosimilars as well as follow-on biologic insulins are in development and are expected to be submitted for approval in the future.

**FOLLOW-ON BIOLOGICS VS GENERICS**

Follow-on biologics are often incorrectly referred to as biogenerics, biocopies, bioidenticals, or other terms that imply they are generic drugs. Follow-on biologics are very different from small-molecule generics, although they share 2 key similarities. First, both were developed to provide lower-cost medication alternatives. Second, to be approved by the FDA, both
must demonstrate physical and/or chemical characteristics in
comparison to their previously approved reference product.

Beyond that, there are numerous differences between
generic drugs and follow-on biologics (TABLE 3). These are primarily due to differences in the manufactur-
ing process and the structural differences between small-
molecule generics and large-molecule biologics (FIGURE 3).
In contrast to generic molecules, follow-on biologics are not
identical copies of the reference product. All generics, unlike
follow-on biologics, can be fully characterized chemically
and the process of chemical synthesis is relatively straightfor-
ward. Generic drugs are not required to undergo phase 2 or
phase 3 evaluations or to bear the expense of animal and
extensive clinical testing. Consequently, the cost to
develop a generic drug is far less than for its branded refer-
ence product.

Follow-on biologics are produced in living cells or organ-
isms and often rely on recombinant DNA technology. As part of
the evidence developed for their regulatory submission,
biologic molecules must undergo biochemical and physico-
chemical analysis and pharmacokinetic and pharmacody-
namic testing, and provide safety and efficacy data designed
to meet the FDA’s regulatory requirements. Furthermore,
the biological structure of the active substance of a
follow-on biologic is determined to be similar, there is still
no guarantee that the safety and efficacy of the molecule
is sufficiently similar to its reference product. Therefore,
unlike generic drugs, follow-on biologics are required to
undergo phase 3 clinical testing—albeit not as extensive as
that required for the previously approved reference biologic.5
Thus, the expense to develop a follow-on biologic is less than
its reference product, yet much greater than a small-mole-
cule generic.

**Interchangeability, therapeutic equivalence, and substitution**

Interchangeability is a regulatory designation that is differ-
ent from that of biosimilarity. Though the FDA has not issued
specific guidance on interchangeability, it has proposed that
the sponsor of a follow-on biologic would need to demon-
strate, in either pre- or postmarketing studies, that repeated
switches from the follow-on biologic to its reference product
would show no negative effects with respect to safety, effi-
cacy, or immunogenicity.19

Small-molecule generics may be substituted by the
pharmacist if they are rated as therapeutically equivalent.17
Therapeutic equivalence for a generic molecule is established
if it demonstrates bioequivalence to its reference drug.17 At
this time, there are no criteria for establishing therapeutic
equivalence of follow-on biologics approved using the drug
pathway. Therefore, follow-on biologics are not rated as
therapeutically equivalent and cannot be substituted by the
pharmacist without the authorization of the prescriber. The
prescriber retains the right to switch a patient from a follow-
on biologic to its reference biologic product or vice versa, as
this is within the scope of medical practice.

Substitution of biologic medicines by the pharmacist will
require that a follow-on biologic is approved as a biosimilar

**TABLE 2  Biosimilars approved in the United States**

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Reference product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic name</strong></td>
<td><strong>Proprietary name</strong></td>
</tr>
<tr>
<td>Filgrastim-sndz</td>
<td>Zarxio</td>
</tr>
<tr>
<td>Infliximab-dyyb</td>
<td>Inflectra</td>
</tr>
<tr>
<td>Infliximab-dyyb</td>
<td>Remsima</td>
</tr>
<tr>
<td>Etanercept-szzs</td>
<td>Erelzi</td>
</tr>
<tr>
<td>Adalimumab-atto</td>
<td>Amjevita</td>
</tr>
</tbody>
</table>
with a designation of interchangeability. The practice of pharmacist substitution is also regulated by state substitution laws.

**Prescriber considerations regarding follow-on insulin glargine**

As mentioned previously, follow-on biologics represent an evolving strategy to improve patient access to biologic medicines at a lower cost. In Europe, the average price discount for biosimilars compared to the reference biologic product has been 25% to 30%.\(^{20}\) Estimated cost savings associated with follow-on biologics in Europe and the United States could amount to $110 billion in US dollars in 2015-2020.\(^{21}\) As these medications are introduced into primary care, several factors should be kept in mind. Some of those related to the follow-on insulin glargine Basaglar are presented below in an author/clinician exchange, which occurred on August 18, 2016.

**Dr. Wright:** Now that 3 insulin glargine formulations will be available in the United States after December 15, 2016, are there any precautions primary care providers should take when prescribing insulin glargine U-100?

**Dr. Blevins:** Yes, several points should be kept in mind. First, there are distinct pharmacokinetic and pharmacodynamic differences between glargine U-100 and glargine U-300. It is therefore incumbent upon the prescriber to state on the prescription which of the 3 insulin glargine products is desired. The dose of insulin glargine

---

**TABLE 3  Comparison of generic drugs and follow-on biologics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Generic drugs(^{13,17,18})</th>
<th>Follow-on biologics/biosimilars(^{3,5,7,14,15})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
<td>• Small, well-defined molecules (&lt;500 to 900 Daltons)</td>
<td>• Large, complex molecules (usually proteins) with potential structural variations (4000 to &gt;140,000 Daltons)</td>
</tr>
<tr>
<td></td>
<td>• Identical to reference product</td>
<td>• Highly similar to reference product</td>
</tr>
<tr>
<td></td>
<td>• Mostly without a device</td>
<td>• Device is often a key differentiator from the reference product (eg, insulin pen in the case of insulins)</td>
</tr>
<tr>
<td></td>
<td>• Predominately oral delivery</td>
<td>• Predominately parenteral delivery</td>
</tr>
<tr>
<td></td>
<td>• Immunogenicity is not an issue</td>
<td>• Immunogenicity must always be evaluated</td>
</tr>
<tr>
<td><strong>Development</strong></td>
<td>• Able to prove identical structure to reference product through analytical characterization</td>
<td>• Significant R&amp;D to develop (cell line, manufacturing process, formulation, etc)</td>
</tr>
<tr>
<td></td>
<td>• Very limited clinical trials required (often only phase 1 PK/PD studies in healthy volunteers)</td>
<td>• Emphasis on phase 1 studies in humans and animals to demonstrate highly similar structure, PK, PD to reference product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Phase 3 studies in humans largely to confirm safety relative to reference product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Postmarketing surveillance is required</td>
</tr>
<tr>
<td><strong>Production</strong></td>
<td>• Chemical synthesis</td>
<td>• Genetically modified living organisms</td>
</tr>
<tr>
<td></td>
<td>• Well-characterized by validated analytical methods</td>
<td>• Multiple methods used to characterize</td>
</tr>
<tr>
<td></td>
<td>• Manufacturing changes easily validated</td>
<td>• Highly sensitive to manufacturing changes</td>
</tr>
<tr>
<td></td>
<td>• Relatively low cost to manufacture</td>
<td>• Often comparatively high costs</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>• Relatively stable</td>
<td>• Sensitive to storage and handling conditions</td>
</tr>
<tr>
<td></td>
<td>• Generally low potential for immune reactions</td>
<td>• Higher potential for immune reactions</td>
</tr>
<tr>
<td><strong>FDA Pathway for Approval</strong></td>
<td>• 505(j)</td>
<td>• 505(b)(2) if approved biologic developed under 505(b)(1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 301(k) if approved biologic developed under 301(a)/BLA</td>
</tr>
</tbody>
</table>

**Abbreviations:** BLA, Biologic License Application; FDA, US Food and Drug Administration; PD, pharmacodynamics; PK, pharmacokinetics; R&D, research and development.
should always be expressed in units. Basaglar has not been approved as therapeutically equivalent with Lantus; therefore, Basaglar cannot be substituted for Lantus by the pharmacist and vice versa. Note, however, that neither Basaglar nor Lantus are immune to formulary limitations that may be imposed by integrated health systems or pharmacy benefit managers.

**Dr. Blevins:** I recently had a conversation with a primary care colleague about a 42-year-old patient with type 2 diabetes. The patient has an HbA1c of 6.9% and has been treated for several months with metformin 1000 mg twice daily and 60 units of the Lantus brand of insulin glargine U-100 with dinner. My colleague is considering changing his patient to Basaglar, but isn’t sure how to do it.

**Dr. Wright:** To be approved as a follow-on biologic to Lantus, Basaglar was required to demonstrate similar pharmacokinetic and pharmacodynamic properties, as well as comparable effectiveness to Lantus. This means that Basaglar would be dosed with the same number of units as previously used for Lantus—in this case, 60 units with dinner. If the patient was to be switched from insulin glargine U-300 (Toujeo) to Basaglar, it is recommended in the prescribing information for Basaglar to reduce the initial dose of Basaglar to 80% of the Toujeo dose, or 48 units.

**SUMMARY**

Follow-on biologics are submitted and approved through either an NDA or BLA regulatory pathway. The development program for follow-on biologics is based on the totality of evidence and is supported by a comprehensive preclinical and clinical development process. Insulin, calcitonin, and human growth hormone are 3 classes of biologic drugs that would submit an NDA to advance a follow-on biologic application before March 23, 2020. The approval standards for follow-on biologics are far more stringent than those required for small-molecule generic drugs due to the complex nature of therapeutic proteins. The FDA requirements for demonstrating interchangeability (a regulatory designation that applies to biosimilars only) have not been defined by the FDA, and state laws regarding substitution continue to evolve. Follow-on biologics, including biosimilars, are expected to be a key strategy in lowering cost and increasing patient access to biologics.

In conclusion:
- All biosimilars are considered to be follow-on biologics, but not all follow-on biologics meet the regulatory designation to be a biosimilar.
- Follow-on biologics are complex therapeutic proteins and are more costly to develop than small-molecule, chemically derived generics.
- There is currently no guidance on interchangeability for biosimilars and follow-on biologics like Basaglar, and they are not expected to be substitutable at the pharmacy without prescriber authorization.

**REFERENCES**

Titratable Fixed-Ratio Combinations in Type 2 Diabetes Mellitus: Focus on GLP-1R Agonists Combined With Basal Insulin

James LaSalle, DO, FAAFP; and John R. White, Jr., PA-C, PharmD

CASE STUDY: MA is a 59-year-old male diagnosed with type 2 diabetes mellitus (T2DM) 9 months ago (glycated hemoglobin A1c [HbA1c] 8.8%). Metformin was initiated and titrated to 1000 mg twice daily. His HbA1c now is 7.7%; fasting plasma glucose (FPG) 94-126 mg/dL. Except for hypertension (BP 134/82 on hydrochlorothiazide [HCTZ]) and obesity (weight 220 pounds, body mass index 31.5 kg/m²), he is in otherwise good health. MA comments that, although he is trying to keep a positive attitude about his diabetes, he has found his life challenging since receiving the diagnosis of T2DM.

INTRODUCTION
This case scenario presents a common situation in which the HbA1c remains elevated despite maximal metformin therapy and a normal FPG. The treatment of hyperglycemia in patients without glycemic control despite metformin monotherapy is the focus of this article, with particular focus on the use of fixed-dose (FDC) and fixed-ratio combination products.

BEYOND METFORMIN
There are 2 general approaches that can be taken to achieve glycemic control when metformin therapy is not adequate. One is a sequential approach in which a second medication is added and titrated until glycemic control is achieved. If glycemic control is not achieved within a short period of time, eg, 3 months, and the maximum dose is reached or adverse effects become unacceptable, a third medication is added, with further adjustment as needed. The sequential approach is generally consistent with current recommendations of the America Diabetes Association/European Association for the Study of Diabetes and the American Association of Clinical Endocrinologists/American College of Endocrinology.1,2 The other approach is to initiate combination therapy at the outset in patients with baseline HbA1c who are unlikely to attain their glycemic goal with monotherapy. The threshold baseline HbA1c for initiating combination therapy is generally 9%.1,2

The sequential approach is reasonable provided that medication doses are titrated over a few months and medications are added in a timely fashion when glycemic control has not been achieved. In practice, however, clinical inertia often occurs, leading to delays of months or years in adjusting medications.3,4 As a consequence, patients are unnecessarily exposed to long periods of hyperglycemia, which increases the risks of cardiovascular events in patients with T2DM.5-10 The United Kingdom Prospective Diabetes Study (UKPDS) showed that microvascular complications are related to the severity and duration of hyperglycemia.11,12 This added risk is on top of the increased cardiovascular risk that starts within the normal glucose range and occurs without evidence of a threshold effect.13-17 In fact, a transition from low to high cardiovascular risk has been shown to occur nearly 15 years earlier in patients with T2DM vs healthy controls.18

Additional observations from the UKPDS underscore the importance of early control of hyperglycemia; most noteworthy, benefits of blood glucose control were sustained for up to 10 years after cessation of randomized treatment.19 The importance of this so-called legacy effect has been echoed by investigators and diabetes organizations.20

INDIVIDUALIZING TREATMENT BEYOND METFORMIN
Ten classes of medication are available for use in combination with metformin. The selection of additional therapy is based
on a host of medication, patient, and other factors. Medication factors include mechanism(s) of action that complement metformin and that address pathophysiologic defects, magnitude of additional glycemic lowering, effect on FPG and postprandial glucose (PPG), adverse events, effect on body weight, and durability. Patient factors include comorbidities such as cardiovascular disease and renal dysfunction, hypoglycemic awareness, body weight, and history of medication adherence. Insurance coverage and treatment affordability are important considerations as well.

Although FPG is the primary target of initial treatment with metformin, as the case scenario shows, reducing the FPG to the normal range sometimes does not result in a HbA1c <7.0%. The reason for this persistence in elevated HbA1c is that PPG also contributes to the HbA1c. Whereas a HbA1c >10.2% is primarily determined by the FPG, a HbA1c <7.3% is primarily determined by the PPG. In fact, the FPG and PPG contribute equally when the HbA1c is in the range of 7.3% to 8.4%. Consequently, add-on therapy to metformin that significantly lowers PPG is often desirable.

The case scenario also suggests some degree of clinical inertia by the provider, because 9 months have elapsed since the patient’s diagnosis and the patient’s HbA1c remains above the glycemic target at 7.7%, yet his only treatment is metformin. The patient’s admission that he has found life challenging since the diagnosis of T2DM suggests that he may be experiencing clinical inertia as well. Talking with the patient to identify his concerns and challenges is an important first step in resolving clinical inertia. In this case, asking MA what he has found challenging would be a good place to start. Once identified, many patient factors that contribute to clinical inertia can be quickly resolved. Adding to metformin a medication with a low incidence of hypoglycemia or that does not promote weight gain is often helpful to patients. In addition, combination products may ease patient concerns about pill burden and may lower cost compared with taking the individual medications.

The remainder of this article focuses on the use of existing and emerging combination products for use in the treatment of patients with T2DM. These include FDCs that contain metformin, as well as fixed-ratio combination products.

**METFORMIN FIXED-DOSE COMBINATION PRODUCTS**

Metformin is available in numerous FDCs with the classes of medications with which it is typically used, including dipeptidyl peptidase-4 inhibitor, sodium glucose cotransporter-2 inhibitor, sulfonylurea, and thiazolidinedione (TABLE 1). The impact of an FDC vs individual medications on patient adherence, glycemic control, patient satisfaction, and cost has been evaluated in several mostly retrospective studies.

General findings of these studies indicate that patient adherence decreases when patients move from monotherapy to dual therapy with the individual medications, but the decrease in adherence is small when patients move from monotherapy to an FDC. However, adherence improves when patients move from dual therapy with the individual medications to an FDC. Improved adherence with the FDC has important benefits, including a 0.5% greater reduction in the HbA1c level compared with individual medications. Also, patient satisfaction is higher with an FDC compared with individual medications.

### TABLE 1 Metformin fixed-dose combination products

<table>
<thead>
<tr>
<th>Metformin dose (mg)</th>
<th>Oral agent and dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>Glipizide 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>Glyburide 1.25 mg</td>
</tr>
<tr>
<td></td>
<td>Linagliptin 2.5 mg</td>
</tr>
<tr>
<td>500</td>
<td>Alogliptin 12.5 mg</td>
</tr>
<tr>
<td></td>
<td>Canagliflozin 50 mg</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin 5 mg</td>
</tr>
<tr>
<td></td>
<td>Empagliflozin 5 mg</td>
</tr>
<tr>
<td></td>
<td>Glipizide 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>Glyburide 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone 15 mg</td>
</tr>
<tr>
<td></td>
<td>Repaglinide 1 mg</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone 2 mg</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin 5 mg</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin 50 mg</td>
</tr>
<tr>
<td>850</td>
<td>Linagliptin 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>Pioglitazone 15 mg</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin 50 mg</td>
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<tr>
<td>1000</td>
<td>Alogliptin 12.5 mg</td>
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<tr>
<td></td>
<td>Canagliflozin 50 mg</td>
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<tr>
<td></td>
<td>Dapagliflozin 5 mg</td>
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<tr>
<td></td>
<td>Empagliflozin 5 mg</td>
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<td></td>
<td>Glipizide 2.5 mg</td>
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<tr>
<td></td>
<td>Linagliptin 2.5 mg</td>
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<tr>
<td></td>
<td>Pioglitazone 15 mg</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone 2 mg</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin 50 mg</td>
</tr>
</tbody>
</table>

^aImmediate-release form unless otherwise specified.

^bImmediate-release and extended-release forms available.

^cExtended-release form.
COMBINING A GLP-1RA WITH BASAL INSULIN

Two classes of medications that have taken on a greater recommended role for the management of patients with T2DM are the glucagon-like peptide-1 receptor agonists (GLP-1RAs) and basal insulin.1,2

While the GLP-1RAs reduce both FPG and PPG, the shorter-acting GLP-1RAs (exenatide twice daily and lixisenatide) exert a greater effect on PPG, while the long-acting GLP-1RAs (albiglutide, dulaglutide, exenatide once weekly, and liraglutide) exert a greater effect on FPG.3

In addition to lowering FPG and PPG, the GLP-1RAs produce several other beneficial effects. Among these are a low incidence of hypoglycemia, a mean weight loss of 2.9 kg, mean diastolic and systolic blood pressure reductions of 1.4 mm Hg and 3.6 mm Hg, respectively, and mean total cholesterol reduction of 3.9 mg/dL.4 Recent evidence also indicates that liraglutide results in cardiovascular benefit by virtue of lowering the risk of major adverse cardiovascular events (MACE; i.e., composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) compared with placebo as part of standard care.5 In patients with a myocardial infarction or hospitalization for unstable angina within the previous 180 days, lixisenatide was shown to pose no increased risk vs placebo for the composite endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina.6

For patients with baseline HbA1c >9.0%, a combination of a GLP-1RA and basal insulin, metformin and GLP-1RA, or metformin and basal insulin are recommended treatment options.1,2 A GLP-1RA is generally preferred over prandial insulin because of demonstrated equal or superior glycemic efficacy with weight loss and less hypoglycemia.1 Furthermore, the addition to metformin of a GLP-1RA or basal insulin are 2 of the recommended treatment options for patients with HbA1c ≥7.5% who do not achieve adequate glycemic control with metformin.1,2

TITRATABLE FIXED-RATIO COMBINATIONS OF BASAL INSULIN/GLP-1RA

Two products that combine a basal insulin with a GLP-1RA were approved by the US Food and Drug Administration in November 2016. Both products are titratable. One is the fixed-ratio combination of insulin glargine U-100 and the GLP-1RA lixisenatide that can be titrated to deliver glargine over a range of 15 to 60 units per day in a 3:1 ratio with lixisenatide. The fixed-ratio combination limits the dose of lixisenatide to a maximum of 20 mcg/d. The other is a fixed-ratio combination of insulin degludec U-100 and the GLP-1RA liraglutide that can be titrated over a range of 50 dose units. Each dose unit is a ratio of 1 unit of degludec and 0.036 mg of liraglutide. The maximum daily single administration is 50 units of degludec and 1.8 mg of liraglutide. Use of these fixed-ratio combinations is relatively straightforward, as both products are titrated based on only the basal insulin component to achieve the glycemic target. Titration based on the basal insulin component allows for a slow increase in the dose of the GLP-1RA, thereby reducing the incidence and severity of nausea and vomiting associated with the GLP-1RA.

Insulin glargine/lixisenatide

The fixed-ratio combination of insulin glargine and lixisenatide (IGlariLixi) has been studied in two 30-week trials of patients with T2DM. In the first, IGlariLixi was compared with glargine and lixisenatide given separately to patients with T2DM inadequately controlled on metformin with or without a second oral glucose-lowering medication.7 Patients completed a 4-week run-in phase to stabilize treatment, during which time only metformin was continued and the dose optimized. The HbA1c decreased from 8.2% to 8.1% during the run-in phase.

Subsequently, patients with an HbA1c of 7.0% to 10.0% were randomized to open-label treatment with IGlariLixi, glargine, or lixisenatide 20 mcg/d. Patients randomized to IGlariLixi were started at a dose of 10 units/5 mcg and titrated up to a dose of 40 units/20 mcg; higher doses were administered using IGlariLixi in a ratio of 3:1. The doses of IGlariLixi and glargine were titrated to a maximum of 60 units/d glargine and 20 mcg/d lixisenatide to achieve and maintain an FPG of 80 to 100 mg/dL while avoiding hypoglycemia. The FDC of IGlariLixi provided significantly greater HbA1c and PPG reductions than glargine 100 units/mL or lixisenatide (TABLE 2).

Patients treated with IGlariLixi lost 0.3 kg of body weight compared with a weight gain of 1.1 kg for patients treated with glargine. Significantly more patients reached the HbA1c target <7.0% with IGlariLixi (74% vs 59% vs 33%). Documented symptomatic hypoglycemia (blood glucose <70 mg/dL) was similar with IGlariLixi and glargine, but lower with lixisenatide. Significantly more patients reached the HbA1c target <7.0% with no weight gain and no documented symptomatic hypoglycemia with IGlariLixi than with glargine (32% vs 19%, respectively). The incidence of gastrointestinal (GI) adverse events with IGlariLixi compared with lixisenatide and glargine, respectively, was 9.6% vs 24.0% vs 3.6% for nausea; 3.2% vs 6.4% vs 1.5% for vomiting; and 9.0% vs 9.0% vs 4.3% for diarrhea. Nausea was the most common GI reason for discontinuation, occurring in 0.4%, 2.6%, and 0% of IGlariLixi, lixisenatide, and glargine patients, respectively.

The second trial compared IGlariLixi with glargine in patients inadequately controlled with basal insulin or without up to 2 oral glucose-lowering medications.8 Patients com-
completed a 6-week run-in, during which time glargine was either introduced or continued and stabilized or further titrated, and oral glucose-lowering medications other than metformin were stopped. The HbA1c decreased from 8.5% to 8.1% during the run-in phase. Patients with HbA1c of 7.0% to 10.0%, FPG ≤140 mg/dL, and glargine dose of 20 to 50 units were randomized to 30 weeks of open-label treatment with IGlarLixi or glargine and the doses titrated to a maximum of 60 units/d glargine and 20 mcg/d lixisenatide to achieve and maintain an FPG of 80 to 100 mg/dL while avoiding hypoglycemia.

The fixed-ratio combination of IGlarLixi provided significantly greater HbA1c and PPG reductions compared with glargine 100 units/mL (TABLE 2). Patients treated with IGlarLixi lost 0.7 kg compared with a weight gain of 0.7 kg for patients treated with glargine. Significantly more patients reached the HbA1c target <7.0% with IGlarLixi (55% vs 30%). Patients treated with IGlarLixi experienced fewer events of documented symptomatic hypoglycemia than patients treated with glargine; the rates of severe hypoglycemia were low. Significantly more patients treated with IGlarLixi reached the HbA1c target <7.0% with no weight gain and no documented symptomatic hypoglycemia than with glargine (20% vs 9%, respectively). The incidence of GI adverse events was higher with IGlarLixi than glargine, with nausea causing discontinuation in 1.1% and 0% of patients, respectively.

### Insulin degludec/liraglutide

The fixed-ratio combination of insulin degludec and liraglutide (IDegLira), was studied in a 26-week, randomized, double-blind study with a 26-week extension. Patients with T2DM inadequately controlled with metformin with or without pioglitazone were randomized to IDegLira, degludec, or liraglutide for 26 weeks. IDegLira and degludec were titrated to achieve an FPG of 72 to 90 mg/dL; the maximum daily dose of IDegLira was 50 units of degludec and 1.8 mg of liraglutide. There was no maximum dose of degludec. The dose of single-agent liraglutide was initiated at 0.6 mg/d and titrated to 1.8 mg/d over 2 weeks. In the preplanned extension, patients continued their allocated treatment for an additional 26 weeks.

At the end of 26 weeks, the HbA1c reduction with IDegLira was noninferior to degludec and significantly greater than liraglutide (TABLE 2). The FPG reduction with IDegLira was similar to degludec but greater than with liraglutide. Reductions in the PPG increment after main meals with IDegLira were significantly greater than with degludec.
and similar to liraglutide. Body weight decreased 0.5 kg with IDegLira and increased 1.6 kg with degludec. Significantly more patients treated with IDegLira reached the HbA1c target <7.0% than patients treated with degludec or liraglutide. Significantly more patients treated with IDegLira reached the HbA1c target <7.0% without weight gain or hypoglycemia than patients treated with degludec but not liraglutide (36% vs 14% vs 52%, respectively). Confirmed hypoglycemia (ie, requiring assistance or blood glucose <56 mg/dL) occurred less frequently in the IDegLira group than in the degludec group but more frequently than in the liraglutide group. The incidence of GI adverse events with IDegLira compared with liraglutide and degludec, respectively, was 9% vs 20% vs 4% for nausea; 4% vs 8% vs 1% for vomiting; and 8% vs 13% vs 5% for diarrhea. Discontinuation due to an adverse event occurred in 1.2%, 5.8%, and 1.9% of IDegLira, liraglutide, and degludec patients, respectively.

Results of the 26-week extension confirmed the results of the initial 26-week study, demonstrating the sustainability of the benefits of IDegLira compared with its components in glycemic efficacy, safety, and tolerability.37

The efficacy and safety of IDegLira also has been studied in patients taking basal insulin and metformin with or without sulfonylurea/meglitinide therapy.38 Patients were randomized to IDegLira or degludec; the degludec dose was titrated to achieve an FPG of 72 to 90 mg/dL. After 26 weeks, the HbA1c reduction was significantly greater with IDegLira than with degludec at equivalent insulin doses (Table 2).38 More patients treated with IDegLira achieved HbA1c <7% without any confirmed hypoglycemia during the

| TABLE 2 | Studies of fixed-ratio combinations of insulin glargine/lixisenatide and insulin degludec/liraglutide (continued) |
| --- | --- | --- | --- | --- |
| Population/baseline treatment | Trial treatment | Blood glucose changes from randomization | Weight change | Hypoglycemia (patients/event-year) |
| Insulin degludec/liraglutide | | | | |
| MET ± PIO36 | HbA1c: 8.3% | FPG: 162-169 mg/dL | N=1660 | |
| | MET ± PIO + | IDegLira | Degludec | or | HbA1c: -1.9% vs -1.4% vs -1.3% | -0.5 kg vs 1.6 kg vs -3.0 kg | Confirmed: 1.8 vs 2.6 vs 0.2 |
| | Degludec | or | Liraglutide 1.8 mg/d x 26 weeks | | FPG: -65 mg/dL vs -65 mg/dL vs -32 mg/dL | | Severe: 0.4% vs 0.5% vs 0% |
| | | | | % HbA1c <7.0%: 81% vs 65% vs 60% | | |
| 26-week extension of the above trial37 | N=1311 | | | |
| | MET ± PIO + | IDegLira | Degludec | or | HbA1c: -1.8% vs -1.4% vs -1.2% | -0.4 kg vs 2.3 kg vs -3 kg | Confirmed: 1.8 vs 2.8 vs 0.2 |
| | Degludec | or | Liraglutide 1.8 mg/d x 26 weeks (52 weeks total) | | FPG: -62 mg/dL vs -61 mg/dL vs -30 mg/dL | | Severe: 0.4% vs 0.5% vs 0.5% |
| | | | | % HbA1c <7.0%: 78% vs 63% vs 57% | | Nocturnal: 0.2 vs 0.4 vs 0.02 |
| Basal insulin + MET ± SU/MEG38 | HbA1c: 8.7%-8.8% | FPG: 173-175 mg/dL | N=398 | |
| | MET + | IDegLira | Degludec | or | HbA1c: -1.9% vs -0.9% | -2.7 kg vs 0 kg | Confirmed: 1.5 vs 2.6 |
| | | Degludec × 26 weeks | or | 26 weeks | FPG: -62 mg/dL vs -46 mg/dL | | Severe: 0.5% vs 0% |
| | | | | HbA1c <7%: vs 60% vs 23% | | Nocturnal: 0.22 vs 0.32 |

Abbreviations: BG, blood glucose; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; IDegLira, insulin degludec/liraglutide; IGlarLixi, insulin glargine/lixisenatide; MEG, meglitinide; MET, metformin; OAD, oral glucose-lowering drug; PIO, pioglitazone; PPG, postprandial glucose; SU, sulfonylurea.

1Titrated to achieve a FPG of 80-100 mg/dL to a maximum of 20 mcg/d lixisenatide (if applicable) and 60 units/d glargine with no hypoglycemia.
2Initial dose of 10 mcg/d for 2 weeks, then 20 mcg/d.
3Hypoglycemia defined as typical symptoms with self-measured blood glucose ≤70 mg/dL.
4Hypoglycemia requiring assistance (severe) or episodes in which self-measured blood glucose was <56 mg/dL with or without symptoms.
5Percent of patients.
6Changes from baseline (week 0) to week 52.
7Hypoglycemia occurring between 0001 and 0559 h.
last 12 weeks of treatment with weight gain compared with degludec (40% vs 8.5%, respectively). Overall adverse events, including hypoglycemia, were similar and the incidence of nausea was low in both groups.

SUMMARY
The generally progressive nature of T2DM requires that treatment be intensified to maintain glycemic control. However, delays in treatment intensification are common, thereby unnecessarily exposing patients to complications of hyperglycemia. One strategy to promote treatment adherence is the use of FDC products. Many such products containing metformin with another oral antihyperglycemic agent are available and have shown improved patient adherence compared with the same medications given separately. Glycemic control is improved and patients report greater satisfaction with titratable fixed-ratio combination products consisting of a basal insulin analog and a GLP-1RA were recently approved in the United States based on results of studies showing improved glycemic control and other benefits, such as mitigation of weight gain and fewer GI adverse events, compared with the same medications given separately.

REFERENCES
2. Garber AJ, Abrahamson ML, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm — 2016 Executive Sum-
3. Khunti K, Wolden ML, Thorstet B, Anderssen M, Davies MI. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Dia-
5. Paul SK, Klein K, Thorstet B, Wolden ML, Khunti K. Delay in treatment intensifica-
tion increases the risks of cardiovascular events in patients with type 2 diabetes. Car-
diovasc Diabetol. 2015;14:100.
6. Shah AD, Langenbarg C, Rosamagnani E, et al. Type 2 diabetes and incidence of car-
diovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocri-
nology. 2015;3(2):105-113.
10. Chou C, Barner JC, Jaspann KA, Johnson MT. Dose adherence and reimburse-
11. Lokhandwala T, Smith N, Sternhufd C, Sorostadins E, Lee WC, Mukherjee J. A ret-
rospective study of persistence, adherence, and health economic outcomes of fixed-
dose combination vs. loose-dose combination of oral anti-diabetes drugs. J Med Econ.
12. Pan E, Chernew ME, Fendrick AM. Impact of fixed-dose combination drugs on adher-
14. Williams SA, Boysman EK, Hultbet IM, Bergesson JG, Zhang B, Graham J. Hemsiglo-
bin A1c outcomes and health care resource use in type 2 diabetes mellitus patients treated with combination oral antidiabetic drugs through step therapy and loose-
16. Han S, Iglay K, Davies MI, Zhang Q, Radacin L. Glycemic effectiveness and medica-
tion adherence with fixed-dose combination or coadministered dual therapy of anti-
20. Marno SF, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular out-
23. Aroda VR, Rosenstock I, Wyscam C, et al. Efficacy and safety of LixiLan, a titratable fixed-dose combination of insulin glargin plus lixisenatide in type 2 diabetes inade-
25. Gough SC, Iode BW, Woot WC, et al. One-year efficacy and safety of a fixed combina-
tion of insulin degludec and liraglutide in patients with type 2 diabetes: results of a 26-
week extension to a 26-week main trial. Diabetes Obes Metab. 2015;17(10):945-973.
Diagnosis of Cirrhosis and Evaluation of Hepatic Encephalopathy: Common Errors and Their Significance for the PCP

Steven L. Flamm, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES
1. Identify strategies to improve early detection of liver cirrhosis and its complications
2. Describe the evidence linking alterations in the human microbiome with liver disease and complications such as hepatic encephalopathy
3. Describe results of preliminary investigations showing improved health outcomes in patients with liver cirrhosis managed with treatments intended to restore the gut microbiome

FACULTY DISCLOSURES
Dr. Flamm discloses that he is on the advisory board and speakers’ bureau for Salix Pharmaceuticals.

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CIRRHOSIS – EPIDEMIOLOGY AND UNDERRECOGNITION
Cirrhosis has become the focus of greater attention in recent years largely because of the increasing prevalence of 2 of its most common causes: chronic viral hepatitis and steatohepatitis (a subset of nonalcoholic fatty liver disease [NAFLD]).

Cirrhosis is the result of progressive destruction and regeneration of the liver parenchyma due to chronic liver disease (CLD). Cirrhosis may be more common than previously thought, with an estimated prevalence of 0.27% in adults in the United States, according to data from the National Health
and Nutrition Examination Survey (NHANES). The 2-year mortality rate is estimated to be 26.4%. Surprisingly, 69% of adults with cirrhosis assessed in NHANES reported they were unaware of having liver disease, highlighting the possibility of many undiagnosed cases of cirrhosis.

One of the largest risk groups for CLD are people with NAFLD, which afflicts approximately 30% to 40% of the population and is projected to become the single most common indication for liver transplantation in the United States over the next 2 decades. However, the results of a 2013 survey suggest that the importance of NAFLD appears to be under-recognized among primary care providers (PCPs). The survey results showed that less than half of PCPs screened patients with diabetes and obesity for NAFLD and only one-quarter of PCPs referred patients with NAFLD to a hepatologist for evaluation.

This underdiagnosis of cirrhosis may be compounded by the use of liver function enzyme blood tests as the basis for current strategies to identify liver disease in the general population, even though they are nonspecific markers of liver injury and may be normal in patients with significant liver disease. One study of 504 patients with risk factors for cirrhosis showed that 72% of patients with elevated liver stiffness (ie, diminished elastic property of liver tissue), 60% (12 of 20) with liver fibrosis on biopsy, and 91% (10 of 11) diagnosed with cirrhosis had a normal alanine aminotransferase (ALT).

In addition, the general absence of symptoms in early stages of liver disease often delays diagnosis. Compensated cirrhosis is defined by the development of clinically evident complications of liver disease (eg, esophageal varices, ascites, jaundice, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, hepatocellular carcinoma). Patients with compensated cirrhosis do not have symptoms related to their cirrhosis and are often not recognized until these complications manifest. At that point, median survival for decompensated cirrhosis is reduced drastically (<2 years vs >12 years for compensated cirrhosis).

Because PCPs are the first medical contact for the majority of patients, they can play a key role in identifying patients who are at risk for, or who have symptoms due to, CLD. They can also collaborate with the specialist in managing and preventing cirrhosis-related complications, such as screening for hepatocellular carcinoma, which is vital, as early detection is associated with a high rate of cure.

**CLINICAL PEARLS FOR DETECTING CIRRHOSIS**

The clinical presentation of patients with cirrhosis, even those with severe disease, is often asymptomatic, with a completely normal or only mildly abnormal liver panel. Moreover, patients can have cirrhosis and feel well early in the course of the disease, although their quality of life may be affected. When patients become symptomatic, it is often too late to reverse the clinical course. For these reasons and to facilitate early intervention, PCPs are encouraged to identify patients at risk for cirrhosis and to be vigilant for subtle signs and symptoms so that a diagnosis can be made before the development of serious complications, such as hepatocellular carcinoma or esophageal and gastric varices. Subtle signs and symptoms include abdominal swelling, elevated ALT or aspartate aminotransferase (AST)/ALT ratio, platelet count <150,000/L, elevated alkaline phosphatase, bilirubin >1.1 mg/dL, serum albumin <2.5 g/dL, and prothrombin time <100%.

Risk factors for cirrhosis in the patient’s medical history merit attention. These include body mass index (BMI), presence of diabetes mellitus or hyperlipidemia, other autoimmune disease, family history of liver disease, sexual orientation, history of intravenous drug abuse (even in the remote past), history of blood transfusion in the remote past, and history of significant alcohol use (even in the past).

Measurement of the serum ammonia level is generally to be avoided, since it is rarely helpful for diagnosis or assessment of treatment response. Thrombocytopenia (platelet count <150 x 10³/L) is often an incidental finding on routine laboratory testing, but it is often indicative of portal hypertension and cirrhosis, even in the absence of an abnormal liver panel. In a study of 223 patients with low platelets, liver disease was the cause in 92 (42%), including 19 with no or mild abnormalities in the liver panel. Elevation of serum prothrombin time or International Normalized Ratio (INR) may indicate hypoalbuminemia or a decreased ability of the liver to synthesize clotting factors. However, these are uncommon findings in compensated cirrhosis.

Given the high disease burden of NAFLD in patients with metabolic syndrome or diabetes, obtaining a random ALT and AST in these patients may be reasonable, since up to 80% of patients with nonalcoholic steatohepatitis (NASH; the subset of NAFLD patients most likely to develop cirrhosis or hepatocellular carcinoma) may be identified based on elevated transaminases. Alkaline phosphatase and/or gamma-glutamyltransferase may be mildly elevated, but bilirubin typically remains normal unless advanced disease is present. It is important to keep in mind that normal liver function tests (LFTs) do not rule out cirrhosis.

Other patients in whom CLD should be suspected despite a normal liver panel are those with “CLD stigmata” (ie, vascular spiders, palmar erythema, and muscle wasting). A palpable left liver lobe, hepatomegaly, and splenomegaly may also be suggestive of cirrhosis.

Liver biopsy is the gold standard for diagnosing and staging liver fibrosis but has several limitations: invasiveness, cost, poor patient acceptance, and risk of complications.
Several noninvasive imaging and laboratory-based tests for diagnosis and staging of fibrosis have been developed, including elastography techniques, which measure mechanical property (stiffness) of liver. Ultrasound, computed tomography, and magnetic resonance imaging have been applied with varying degrees of success. Fibrosis can also be detected using noninvasive scoring systems that utilize different combination of serum surrogate markers for liver disease, eg, Fibrosis-4 (FIB-4) index, AST-to-platelet ratio index (APRI), and the BMI, AST/ALT ratio, diabetes (BARD) score.

Patients diagnosed with cirrhosis should undergo liver cancer screening semiannually with liver imaging using ultrasound. In addition, endoscopy should be performed. If moderate to large varices are present, a non-cardioselective beta-blocker is indicated to prevent variceal bleeding; the patient also should be instructed to avoid aspirin and non-steroidal anti-inflammatory drugs. Protein intake generally is limited to 1 g/kg of body weight.

### DETECTING HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (HE) is a common and major complication of cirrhosis that impacts quality of life, increases the risk of accidents, and is associated with significant morbidity and mortality. Hepatic encephalopathy encompasses a spectrum of cognitive and motor abnormalities that range from minimal deficits, detected only with psychometric or neuropsychological tests and possibly subtle personality changes reported by caregivers (covert HE [CHE]), to progressively greater disturbances in cognition and motor dysfunction (overt HE [OHE]), to coma (TABLE). The neuronal dysfunction of HE is due to hyperammonemia, which is a consequence of impaired metabolic capacity of the urea cycle in the liver and intra- and extra-hepatic portosystemic shunting of blood related to portal hypertension.

The number of hospitalizations associated with a diagnosis of HE has increased approximately 10% annually, with more than 610,000 hospital discharges for patients with HE in 2014. In one study, an estimated 50% of cirrhotic patients had underlying CHE, and 30% developed an episode of OHE over 13 months. Once OHE occurs, patients have a 40% risk for recurrence within 1 year despite standard treatment with lactulose. OHE is associated with diminished survival (40%-50% at 1 year and approximately 20% at 3 years).

Symptoms of HE, graded by the West Haven Criteria (WHC), are relatively nonspecific (TABLE), making a definitive diagnosis of HE challenging. Consequently, HE remains a diagnosis of exclusion. The patient history should focus on changes in cognition, behavior, sleep patterns, work performance, and driving performance. A caregiver may be able to provide history to assist a PCP in detecting changes. A physical examination should evaluate patients for the presence of stigmata of cirrhosis and asterixis. Other causes of encephalopathy should be excluded (eg, electrolyte disturbances, hypoglycemia, uremia, sepsis, thyroid dysfunction). Obtaining ammonia levels is generally not recommended, given the limited utility of a single value in the diagnosis of HE and the nonspecificity of elevated ammonia levels for HE.

PCPs play an important role in identifying the condition because they will often see the patients when HE is in its early stages, and its neuropsychiatric manifestations are subtle. As PCPs are also likely to see patients more frequently and over a longer span of time than specialists, they are more likely to recognize these subtle changes.

### TABLE: Clinical description of hepatic encephalopathy based on West Haven Criteria

<table>
<thead>
<tr>
<th>WHC including MHE</th>
<th>ISHEN</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unimpaired</td>
<td></td>
<td>No encephalopathy at all, no history of hepatic encephalopathy</td>
</tr>
<tr>
<td>Minimal</td>
<td>Covert</td>
<td>Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change</td>
</tr>
<tr>
<td>Grade I</td>
<td></td>
<td>Trivial lack of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction, altered sleep rhythm</td>
</tr>
<tr>
<td>Grade II</td>
<td></td>
<td>Lethargy or apathy, disorientation for time, obvious personality change, inappropriate behavior, dyspraxia, asterixis</td>
</tr>
<tr>
<td>Grade III</td>
<td>Overt</td>
<td>Somnolence to semi-stupor, responsiveness to stimuli, confusion, gross disorientation, bizarre behavior</td>
</tr>
<tr>
<td>Grade IV</td>
<td></td>
<td>Coma</td>
</tr>
</tbody>
</table>

Abbreviations: ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; MHE, minimal hepatic encephalopathy; WHC, West Haven Criteria.

Given the poor prognosis associated with the development of OHE, prompt detection, workup, and referral are vital to allow for early initiation of appropriate management (FIGURE).28 The most important step in the management of HE is identification and treatment of precipitating factors (eg, infections, gastrointestinal [GI] bleeding, overdiuresis, vomiting/diarrhea, electrolyte disorder, constipation).29 Medications used to treat HE are primarily directed at reducing serum ammonia levels.

**GUT MICROBIOME IMPLICATIONS FOR THE TREATMENT OF HEPATIC ENCEPHALOPATHY**

The pharmacologic basis for some of the treatments for HE is supported by a growing body of evidence regarding the interactions between the gut microbiome and its human host. The human microbiome is the collective genome (ie, genetic material) of the more than a thousand microorganisms living in association with the human body, the vast majority of which reside in the distal gut.22,23 This ecological system interacts with internal and external factors to help maintain overall health of the individual.24 Much of our current knowledge in this area comes from the Human Microbiome Project and Human Gut Microbiome Initiative—programs focused on identifying and characterizing gut microorganisms found in healthy and diseased humans.22,23

In selected conditions, including inflammatory bowel diseases, NAFLD, obesity, type 2 diabetes mellitus, and cirrhosis, changes in the composition of the gut microbiota and proinflammatory activities are thought to contribute to disease pathophysiology.22 The altered gut microbiota (dysbiosis) associated with cirrhosis contributes to hyperammonemia and a systemic pro-inflammatory milieu that can potentiate neuroinflammation, brain edema, and neuronal dysfunction.25 With the progression of cirrhosis, it is hypothesized that the hyperammonemia and the pro-inflammatory potentiation occur via the relative reduction in autochthonous (indigenous) commensal organisms and the increase in microbes such as Enterobacteriaceae and Streptococcaeae, which can produce endotoxin and ammonia through their urease activity, respectively.25 While knowledge is evolving regarding various other mechanisms that may contribute to dysbiosis and its functional consequences for liver disease, our current understanding helps inform treatment approaches for hepatic encephalopathy.26

**TREATMENT OPTIONS FOR HEPATIC ENCEPHALOPATHY**

**Probiotics**

Probiotics are live, nonpathogenic microbiologic dietary supplements that alter the intestinal microflora environment. A 2016 meta-analysis of probiotics for management of CHE or OHE included 14 trials and 1152 patients.27 Probiotics had no impact on the overall mortality compared to either lactulose or no treatment/placebo. When probiotics were compared to no treatment/placebo, they were associated with significant improvement in minimal HE (MHE) (odds ratio [OR], 3.91; 95% confidence interval [CI], 2.25-6.80; P<.00001), decreased hospitalization rates (OR, 0.53; 95% CI, 0.33-0.86; P=.01) and decreased progression to OHE (OR, 0.40; 95% CI, 0.26-0.60; P<.0001). Compared to lactulose, however, probiotics did not show a significant difference in any of these outcomes.

Although the mechanisms of HE improvement remain somewhat uncertain, probiotics may act by decreasing colonization by pathogenic bacteria, blocking epithelial attachment, decreasing the production and absorption of ammonia, and altering gut permeability.28

A 2011 Cochrane review of probiotics for patients with HE included 7 trials and 550 patients.29 Compared to no treatment, probiotics were associated with reduced plasma ammonia levels but no significant differences in all-cause mortality, recovery from HE, adverse events, quality of life, or change of/withdrawal from treatment. Compared to lactulose, probiotics were associated with no differences in lack of recovery, adverse events, change of/withdrawal from treatment, plasma ammonia concentration, or change in plasma ammonia concentration.29 For these reasons and because of the wide variability in the content of probiotics, probiotics are not currently recommended as treatment for HE.

**DIETARY MODIFICATION**

Protein calorie malnutrition is a common occurrence in patients with HE and is associated with poor prognosis.30 Contributors include frequent body fluid removal via paracentesis, anemia from GI bleeding, and low-protein diets (previously recommended based on the presumption that they led to reduced ammonia production).14,18

Maintaining adequate protein intake is essential to prevent muscle wasting, as skeletal muscle is the next largest site of ammonia metabolism after the liver.18 For patients with HE, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) recommends that the daily energy intake should be 35 to 40 kcal/kg ideal body weight with daily protein intake of 1.2 to 1.5 g/kg ideal body weight.30 Meals should be small and evenly distributed during the day, with a late-night snack of complex carbohydrates to help minimize protein utilization. Patients should be encouraged to adhere to diets rich in vegetable and dairy protein. Branched-chain amino acid supplements may be of value in patients intolerant of dairy protein. Increasing dietary fiber may also be beneficial.30
LACTULOSE

Nonabsorbable disaccharides, primarily lactulose, have been the mainstay of treatment for HE. Lactulose is degraded by microbiota in the colon to short-chain organic acids, resulting in an acidic environment and an osmotic gradient in the intestinal lumen. The acidic environment is thought to reduce ammonia-producing bacteria and to convert ammonium to nonabsorbable ammonium. The laxative effect results in intestinal cleansing via removal of excess fecal nitrogen.

Lactulose is usually initiated with an oral dose of 30 mL to 45 mL every 1 to 2 hours to produce at least 2 soft bowel movements per day; it is then titrated to a goal of 2 to 3 soft bowel movements a day. Common adverse events of lactulose include flatulence, abdominal discomfort, and diarrhea.

Lactulose has demonstrated variable efficacy in trials (mostly small and underpowered) of patients with HE, but a recent Cochrane review including 38 trials and 1828 patients determined that nonabsorbable disaccharides may be associated with beneficial effects on clinically relevant outcomes compared to placebo/no intervention. These effects included mortality (relative risk [RR], 0.59; 95% CI 0.40-0.87) and reduction of serious complications associated with the underlying liver disease (liver failure, hepatorenal syndrome, and variceal bleeding; RR, 0.47; 95% CI, 0.36-0.60).

ANTIBIOTICS

The rationale for using antibiotics for cirrhosis is to diminish deaminating enteric bacteria, thus decreasing the production and absorption of ammonia and endotoxins. Neomycin and metronidazole have been used for the treatment of OHE, but limited efficacy and adverse events limit their use. Rifaximin is another antibiotic approved by the US Food and Drug Administration for reducing the risk of OHE recurrence in adults. Rifaximin is a poorly absorbed oral antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and anaerobic enteric bacteria that inhibits bacterial protein synthesis.

The 2014 guidelines issued by the American Association for the Study of Liver Diseases/European Association for the Study of the Liver recommend the addition of rifaximin for...
prevention of OHE recurrence in patients who have experienced ≥1 bouts of OHE while on lactulose treatment.15

In a phase 3 trial to assess the efficacy of rifaximin for prevention of HE in high-risk patients, 299 patients in remission from recurrent HE were randomized to receive placebo or rifaximin 550 mg twice daily for 6 months.34 Rifaximin significantly reduced the risk of another HE episode (hazard ratio [HR], 0.42; 95% CI, 0.28-0.64; P < .001), and of hospitalization involving HE (HR, 0.50; 95% CI, 0.29-0.87; P = .01).34 More than 90% of patients in each treatment group received concomitant lactulose therapy, and the adverse event rate was similar between placebo and rifaximin groups.

Although rifaximin is not currently approved for treatment of OHE, 14 of 19 trials included in a 2014 meta-analysis compared rifaximin to either placebo or active treatment (primarily lactulose or lactitol).35 Rifaximin increased the proportion of patients who recovered from OHE (RR, 0.59; 95% CI, 0.46-0.76), reduced mortality (RR, 0.68; 95% CI, 0.48-0.97), and had a beneficial effect on secondary prevention of OHE (RR, 1.32; 95% CI, 1.06-1.65). This latter benefit is important since readmission for HE is common. A study that assessed the combination of rifaximin plus lactulose vs lactulose alone for the treatment of OHE showed the combination to be superior in terms of complete reversal of HE (76% vs 50.8% of patients; P < .004), decreased mortality (primarily due to sepsis) (23.8% vs 49.1%; P < .004), and shorter hospital stay (5.8 ± 3.4 vs 8.2 ± 4.6 days; P = .001).36

CONCLUSION

Cirrhosis is more common than previously thought. Because the liver panel is often normal and the clinical presentation is often asymptomatic, detection of cirrhosis at its earliest stages is often missed in the primary care setting. Consequently, PCPs are encouraged to identify patients at risk for cirrhosis and to be vigilant for subtle signs and symptoms before the development of serious complications, such as hepatic encephalopathy. Treatment has typically been directed at reducing serum ammonia levels. Our evolving knowledge about the pathophysiologic role of gut microbiota disturbances in liver disease, and specifically hepatic encephalopathy, has prompted the development and use of treatments aimed at manipulation of the gut microbiota.

REFERENCES

Role of the Microbiome in Disease: Implications for Treatment of Irritable Bowel Syndrome

Brian E. Lacy, PhD, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES:
1. Describe the findings of the Human Microbiome Project and Gut Microbiome Initiative
2. Describe the evidence linking alterations in the human microbiome with disease, including irritable bowel syndrome
3. Describe results of treatments that act upon the gut microbiota in patients with irritable bowel syndrome

TARGET AUDIENCE
Family physicians and clinicians who wish to gain increased knowledge of the gut microbiome and its implications in the primary care management of IBS.

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Boehringer Ingelheim GmbH; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; and Novo Nordisk Inc. He is on the advisory boards for Abbott Diabetes Care Inc.; Allergan; Becton, Dickinson and Company; Cempra, Inc.; Intarcia Therapeutics, Inc.; and Mylan N.V.
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INTRODUCTION
As many as 1 in 5 Americans have symptoms of irritable bowel syndrome (IBS), but only about 30% seek medical attention.1,2 Even so, IBS accounts for approximately 12% of visits to primary care physicians and 28% of referrals to gastroenterologists.3 With emerging evidence to support some practices, many people with IBS turn to complementary health practices, including dietary manipulation and the use of alternative medicine such as probiotics and prebiotics, to help relieve their symptoms.1,4,5 Therefore, patients with IBS of alternative medicine such as probiotics and prebiotics, to help relieve their symptoms.1,4,5 Therefore, patients with IBS who seek medical care for their IBS symptoms may have questions about diet and alternative treatments or may be self-managing.

Dietary and some other treatments for IBS are supported by a growing body of evidence, much of which comes from programs such as the Human Microbiome Project and Human Gut Microbiome Initiative, which were intended to identify and characterize microorganisms found in association with both healthy and diseased humans. These programs used state-of-the-art technology to characterize the human microbiome from multiple body sites.6 This evidence indicates that the gut microbiome plays an important role in IBS and some other gastrointestinal (GI) disorders. The human microbiome is the collective genome (ie, genetic material) of all the microorganisms living in association with the human body, the vast majority of which reside in the distal gut.7,8 The gut microbiota refers to the complex ecosystem of more than a thousand microbial species inhabiting the intestine, most of which are bacteria, and accounts for 60% of the fecal biomass.6,9,10 While research is still in its infancy, these programs suggest that microorganisms carry out a range of biological functions critical to the health of the individual.7

Emerging evidence also suggests that changes in the composition of the gut microbiota (dysbiosis) correlate with numerous diseases, including type 1 and type 2 diabetes, obesity, asthma, and several cancers, as well as anxiety and depression.7,12-15 Perhaps least surprising is the increasing evidence implicating gut microbiota alterations in gastrointestinal diseases such as inflammatory bowel disease and IBS.16

IRRITABLE BOWEL SYNDROME
Microbial complications of IBS
The most convincing evidence that suggests gut microbiota are involved in the pathogenesis of IBS is the finding that IBS can develop in predisposed individuals following a bout of infectious gastroenteritis.17 The odds of developing IBS are increased more than sixfold after an acute GI infection, and the onset of new IBS symptoms after a bout of infectious gastroenteritis is reported by 6% to 18% of IBS patients.17

Additional evidence supporting a role for the gut microbiota in IBS include differences in the colonic microbiota between IBS and non-IBS populations, symptomatic response of IBS to antibiotic and probiotic administration, and recent anecdotal reports of responses to fecal microbial transplantation.11,18-21 Numerous studies have reported differences in the mucosal and/or fecal microbiota of patients with IBS compared with healthy controls, such as reduced diversity of the microbial population, altered proportion of specific bacterial groups, different degree of variability in the microbiota composition, a higher degree of temporal instability, and more abundant mucosal bacteria.22 Some patients experience small intestinal bacterial overgrowth (SIBO), a condition in which bacteria colonize the small intestine, creating localized inflammation, altering intestinal absorption, and potentially using nutrients needed by the body, which in turn causes malnourishment.

While our understanding of the pathophysiologic role of the gut microbiota in IBS is still developing, several possible mechanisms have been proposed. The current working hypothesis is that altered composition and metabolic activity of the gut microbiota activate mucosal innate immune responses and inflammation.9,17 These processes, in turn, increase mucosal permeability, promote epithelial barrier dysfunction, activate nociceptive sensory pathways, and dysregulate the enteric nervous system.

Treatment approaches focused on altering the gut microbiome
While our knowledge about the gut microbiome and its role in IBS pathophysiology continue to develop, the gut microbiota has been a therapeutic target for years, if not decades.17

Dietary modification
Diet has been shown to significantly influence the composition and metabolic activity of the gut microbiota. In fact, dietary modification can substantially alter the gut microbiome in as...
little as 3 days.\textsuperscript{9,23-25} Additionally, 60% to 70% of patients with IBS report a worsening of symptoms after meals, and 50% to 70% report intolerance to various foods.\textsuperscript{3}

The most compelling evidence for a beneficial impact of diet on IBS exists for a diet that restricts a group of short-chain carbohydrates known collectively as fermentable oligo-, di-, and mono-saccharides and polyols (FODMAPs). FODMAPs are found in such foods as wheat, legumes, milk, some fruits, and sorbitol.\textsuperscript{4,26} Rapid fermentation of these incompletely absorbed carbohydrates leads to gas production and increased luminal water content, resulting in luminal distention that may account for IBS symptoms.\textsuperscript{4} Implementation of a low FODMAP diet for IBS reduces overall gastrointestinal symptoms and individual symptoms such as abdominal pain, bloating, constipation, diarrhea, abdominal distention, and flatulence.\textsuperscript{26,27} In a randomized, single-blind, crossover study of 30 patients with IBS and 8 healthy controls who received 21 days of either a low FODMAP or typical Australian diet, 70% of patients with IBS experienced improvement in overall GI symptoms.\textsuperscript{29} Dietary intervention guided by specialized dietitians appears to be vital for the success of the diet, which is fairly complex.\textsuperscript{28} The ideal length of time for a patient to adhere to a low FODMAP diet has not been adequately studied; however, strict adherence to a low-FODMAP diet is not recommended long-term due to potential risks of inadequate nutrient intake.\textsuperscript{26}

Very limited data suggest that gluten may exacerbate IBS symptoms in patients with IBS but not celiac disease whose symptoms are already controlled on a gluten-free diet. This observation suggests that a gluten-free diet may help some patients with IBS.\textsuperscript{29} However, a more recent study by the same investigators demonstrated that implementation of a gluten-free diet in patients with IBS already on a low FODMAP diet did not provide added benefit.\textsuperscript{30}

Fiber has long been considered a mainstay of therapy for relief of IBS symptoms. The beneficial effects of fiber are thought to reflect colonic fermentation with production of short-chain fatty acids or its action as a prebiotic.\textsuperscript{3} A recent systematic review and meta-analysis of 14 trials found moderate-quality evidence that soluble fiber—but not bran fiber—is effective at improving global IBS symptoms and should remain a first-line therapy for IBS, given its affordability and safety.\textsuperscript{31}

**Probiotics and prebiotics**

Prebiotics (eg, fructooligosaccharides and inulin) are ingredients in food that remain undigested and which may stimulate either the growth or the activity of bacteria that are also beneficial to human health.\textsuperscript{19} In contrast, probiotics are live microorganisms that, when ingested in adequate amounts, confer a health benefit to the host.\textsuperscript{4} Symbiotics combine prebiotics and probiotics, with a potentially synergistic action.\textsuperscript{19} There is a paucity of evidence for the efficacy of prebiotics or symbiotics in IBS.\textsuperscript{22}

Probiotics, principally those containing *Lactobacillus sp.* and *Bifidobacterium sp.*, have been studied extensively as a way to beneficially modulate the GI microbiota in the treatment of IBS.\textsuperscript{17,19,32,33} *Lactobacillus sp.* and *Bifidobacterium sp.* modulate several mechanisms that might be implicated in the pathogenesis of IBS, including effects on intestinal microbiota composition, GI dysmotility, visceral hypersensitivity, altered gut epithelium and immune function, and luminal metabolism.\textsuperscript{22} Interpreting results from probiotic studies in IBS is challenging due to inclusion of patients with different IBS subtypes and the use of multiple probiotic strains and doses across studies, which may obscure the beneficial effects of individual strains within that species.\textsuperscript{19,32}

In a meta-analysis of 35 studies of probiotics vs placebo for IBS, the persistence of IBS symptoms with probiotics was lower, with a relative risk of 0.79 (95% confidence interval, 0.70-0.89). Probiotics reduced abdominal pain, bloating, and flatulence. The number needed to treat (NNT) was 7. Some combinations of probiotics were superior to individual species or strains, although no specific combination was superior to another.\textsuperscript{19} Adverse events were more common with probiotics (16.5%) compared with placebo (13.8%), with a number needed to harm (NNH) of 35.\textsuperscript{35}

**Antibiotics**

The alteration of the gut microbiota, and particularly the possible role of an SIBO in at least some patients with IBS, has prompted the evaluation of antibiotics as a treatment for IBS.\textsuperscript{22} Neomycin, a nonabsorbable antibiotic, was the first investigated for IBS. Neomycin produced a 50% improvement in global IBS symptoms compared with placebo, but also induced rapid bacterial resistance.\textsuperscript{22}

The rifamycin-derivative rifaximin is an oral, nonsystemic, broad-spectrum antibiotic associated with a low bacterial resistance profile and a favorable side-effect profile.\textsuperscript{20} Rifaximin appears to have anti-inflammatory, host-response, and gut microbiota modulatory activities.\textsuperscript{34} Rifaximin has shown efficacy in several small-scale studies of IBS as well as 2 large-scale, identically designed, phase 3, double-blind, placebo-controlled, multicenter trials (Targeted non-systemic Antibiotic Rifaximin Gut selective Evaluation Treatment [TARGET] 1 and TARGET 2) (TABLE).\textsuperscript{20,35}

In TARGET 1 and TARGET 2, patients affected by IBS without constipation (N=1258) received either rifaximin 550 mg or placebo 3 times daily for 2 weeks, then were fol-
followed for an additional 10 weeks.20 Significantly more patients in the rifaximin group than in the placebo group had adequate relief of global IBS symptoms during the first 4 weeks after treatment (TABLE).20,35 The percentage of patients with adequate relief decreased over time in both groups, but remained higher for patients treated with rifaximin compared with patients receiving placebo during all 3 months in both studies. The incidence of adverse events was similar in the rifaximin and placebo groups.

Most recently, the randomized, placebo-controlled TARGET 3 study indicated that repeat treatment with rifaximin 550 mg 3 times daily for up to three 2-week cycles in patients with diarrhea-predominant IBS (IBS-D) was significantly more efficacious than placebo (38.1% vs 31.5%, \( P=0.03 \)) in improving IBS symptoms. Treatment was well tolerated.35

Although not indicated for IBS-C (constipation predominant), rifaximin (400 mg 3 times daily for 7-10 days) has been evaluated in patients with IBS-C in 2 small, double-blind trials.36 In one trial, rifaximin plus neomycin significantly improved severity of constipation and symptoms of bloating and straining for up to 4 weeks compared with neomycin plus placebo.36 In the other trial, which utilized a crossover design, rifaximin significantly decreased bloating, abdominal pain, abdominal distension, and flatulence compared with placebo.37

Overall, these data suggest that rifaximin, with its favorable safety profile and demonstrated efficacy, is a therapeutic option for patients with IBS-D.

**Other prescription medications**

Alosetron, a selective 5-HT\(_4\) antagonist, and eluxadoline, a mixed opioid receptor agonist/antagonist, are also approved for IBS-D but have no effect on the gut microbiome.

**Fecal microbiota transplantation**

Fecal microbiota transplantation (FMT) involves oral administration of encapsulated fecal material containing distal gut microbiota from a healthy person who serves as a donor.14 The goal is to treat disease by restoring microbiota typically found in a healthy person. FMT has been effective for *Clostridium difficile* infection, generating speculation that the process may benefit other conditions associated with dysbiosis, including IBS.14

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**TABLE** TARGET-1, -2, and -3 trials for rifaximin in the management of irritable bowel syndrome²⁰,³⁵

<table>
<thead>
<tr>
<th>Study design</th>
<th>Patients</th>
<th>Treatment</th>
<th>Primary efficacy outcomes</th>
<th>Secondary efficacy outcomes</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>R, DB, PBO-C; TARGET 1 and TARGET 2 combined</td>
<td>IBS (Rome III criteria) with abdominal pain and discomfort</td>
<td>Rifaximin 550 mg tid (n = 624) vs PBO (n = 634) for 2 weeks</td>
<td>Adequate relief of global IBS symptoms: rifaximin vs PBO, 40.7% vs 31.7%; ( P&lt;.001 )</td>
<td>Adequate relief of IBS-related bloating: rifaximin vs PBO, 40.2% vs 30.3%; ( P&lt;.001 )</td>
<td>AEs comparable between groups</td>
</tr>
<tr>
<td>Open label, then R, DB, PBO-C; TARGET 3</td>
<td>IBS-D (Rome III criteria) with abdominal pain and bloating</td>
<td>Rifaximin 550 mg tid open-label for 2 weeks (n=1074) If relapsed during 18-week observation phase: rifaximin 550 mg tid (n=328) vs PBO (n=308)</td>
<td>Percentage of responders after first repeat treatment: rifaximin vs PBO: 38.1% vs 31.5%; ( P=0.03 )</td>
<td>Percentage of responders who did not have recurrence through end of 6-week repeat treatment observation phase and continued to respond without recurrence through end of second repeat treatment phase: rifaximin vs PBO: 13.2% vs 7.1%; ( P=0.007 )</td>
<td>AEs comparable between groups</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; bid, twice daily; DB, double-blind; IBS, irritable bowel syndrome; PBO, placebo; PBO-C, placebo-controlled; R, randomized; TARGET, Targeted non-systemic Antibiotic Rifaximin Gut selective Evaluation Treatment; tid, 3 times daily.

\( ^a \) Patients included in modified intention-to-treat analysis.

\( ^b \) Defined as relief of symptoms for ≥2 of first 4 weeks of treatment by self-report.

\( ^c \) Defined as a decrease in abdominal pain ≥30% from baseline AND a decrease in frequency of loose stools ≥50% from baseline for ≥2 weeks during a 4-week posttreatment period.
Data about the efficacy of FMT for IBS are scanty and far from conclusive at this time, consisting primarily of several case series reporting relief of symptoms in patients with IBS who do not respond to conventional therapy.21,38,39 Among concerns regarding FMT is the potential for long-term risks that may manifest as the development of chronic disease based on alterations in the gut microbiota.14 For example, transplantation of human fecal microbiota from obese subjects to rodents has been shown to transmit an obesity phenotype.40 FMT from lean subjects to obese subjects with metabolic syndrome, on the other hand, has proven beneficial, including an increase in insulin sensitivity.41 Well-designed, large, randomized, controlled studies are required before FMT can be considered a therapeutic option in IBS.

**IMPLICATIONS FOR CLINICAL PRACTICE**

While our understanding of the role of the gut microbiota and dysbiosis in IBS continues to evolve, several treatment approaches that target the gut microbiota have already demonstrated efficacy in IBS. The current body of knowledge regarding these treatments suggests a logical sequence, or simple algorithm, to guide their use in clinical practice (FIGURE).

Diet manipulation should be considered first, including ruling out celiac disease in patients with persistent symptoms of gas, bloating, and diarrhea, as well as patients with a family history.3 A gluten-free diet trial is a reasonable intervention, especially in patients with IBS-D, mixed irritable bowel syndrome, or predominant symptoms of gas and bloating. Alternatively, or in a patient not responding to a gluten-free diet, a 4-week trial of a low FODMAP diet under the guidance of a dietitian may be helpful. Longer trials need careful monitoring due to the potential for nutritional deficiencies.3 Initiative of a gluten-free diet in a patient already on a low FODMAP diet is unlikely to provide additional benefit.

Probiotics may be considered in patients in whom dietary modification provides insufficient relief. While evidence does not suggest superiority of 1 microorganism over another, products containing combinations of microorganisms appear to be slightly more effective than single species/strain products. Trial duration should be at least 4 weeks before assessing treatment response.17

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**FIGURE** Suggested algorithm for gut microbiota-targeted therapy for IBS

- Consider trial of low FODMAP diet or gluten-free diet
  - Adequate relief?
    - Yes: Continue diet
    - No: If tried gluten-free first, switch to low FODMAP diet
  - If tried low FODMAP diet first, gluten-free diet not likely to have additional benefit
    - Continue diet
    - Adequate relief?
      - Yes
      - No: Consider trial of probiotic (combination product)
      - If tried probiotic first, gluten-free diet not likely to have additional benefit
        - Continue probiotic
    - No: Consider 2-week trial of rifaximin 550 mg tid

**Abbreviations:** FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS, irritable bowel syndrome.

*Consider ruling out celiac disease in patients with persistent symptoms of gas, bloating, and diarrhea, and those with a family history.
*Consider at least a 4-week trial at adequate doses before judging response to treatment.
Rifaximin may be considered for patients with IBS refractory to dietary manipulation and probiotics. The drug is indicated only for the treatment of IBS-D, however.

In conclusion, IBS is one of the most common disorders treated by primary care physicians. Our rapidly accumulating knowledge about the pathophysiologic role of disturbances in the gut microbiota in IBS has prompted manipulation of the microbiota as a new therapeutic target for the disorder. A proposed algorithm suggests a logical approach for utilization of diet, probiotics, and antibiotics in clinical practice to manipulate the gut microbiota in the management of patients with IBS.

REFERENCES
Medication Adherence in Type 2 Diabetes Mellitus: Real-World Strategies for Addressing a Common Problem

Stephen A. Brunton, MD, FAAFP; and William H. Polonsky, PhD, CDE

EXTENT OF THE PROBLEM
In 2003, the World Health Organization observed that “increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments.”¹ Evidence since then indicates that medication adherence remains suboptimal for patients with many diseases, including chronic diseases such as type 2 diabetes mellitus (T2DM), for which adherence is reported to range from 30% to 93%.² ³ A meta-analysis that included 40 studies from 2005 to 2015 showed that 67.9% of patients with T2DM were adherent to their oral antihyperglycemic therapy.⁴ A 2015 study reported that the 1-year adherence rate with glucagon-like peptide-1 receptor agonist (GLP-IRA) therapy was 34%.⁵ Adherence with insulin in patients with T2DM has been reported to range from 51% to 59% at 3 months following initiation, 39% to 48% at 6 months, and 27% to 35% at 12 months.⁶

The importance of treatment adherence is well established, as poor adherence contributes to disease progression and increased morbidity and mortality. Analysis of 11,272 veterans with T2DM with a mean follow-up of 5 years showed that for each 10% increase in the medication possession ratio, the mean glycated hemoglobin (HbA1c) decreased by 0.24%.⁷ Poor adherence also leads to increased health care resource utilization and costs, including more frequent hospitalizations.⁸ ⁹ Conversely, while improved adherence decreases medication costs, it can decrease overall health care resource utilization and costs.¹⁰ ¹¹ ¹² Improved medication adherence also contributes to improvement in diabetes-related quality of life.¹³

The potent negative impact of poor medication adherence on diabetes outcomes makes it clear that greater urgency must be given to addressing this issue.¹⁴ ¹⁵ It is not enough to accurately diagnose a disease and prescribe the appropriate treatment; the treatment must be taken. As US Surgeon General C. Everett Koop, MD, once said, “Drugs don’t work in people who don’t take them.” Supporting patients to take their medications is not a “once-and-done” undertaking. It is of utmost importance that treatment adherence be assessed at each patient visit and that appropriate action be taken.

FACTORS CONTRIBUTING TO POOR MEDICATION ADHERENCE
Numerous factors are recognized as contributing to poor medication adherence (TABLE).¹⁹ ⁵⁹ Many of these factors may be interrelated, making it important to identify the root causes. For example, patients may report that they simply forgot to take their medication because of the “busyness” of everyday life when, in fact, they have little intention of taking their medication. This might be because they do not see the need for the medication, are concerned about adverse events, cannot afford it, or have some other reason that overrides the benefit(s) they think would occur by taking their medication.¹⁶ Even the mere act of taking medication on a daily basis can contribute to poor adherence by reminding patients they are sick. Because the factor(s) that contribute to poor adherence vary by individual and over time, it is important to assess patient adherence at each visit.⁶⁰
Another key factor that affects medication adherence is the patient's level of trust in the provider. A cross-sectional analysis of the Diabetes Study of Northern California (N=9377) showed that patients who gave providers lower ratings for eliciting confidence and trust were more likely to have poor adherence. Factors that may have contributed to this finding were providers not involving patients in decisions and not understanding problems patients were having with treatment. Provider behaviors that promote patient trust include active listening, openness, providing emotional support, providing clear and thorough information, and allowing adequate time for patients to ask questions.

THE NEED FOR A PARADIGM SHIFT

Despite efforts to increase patient and provider awareness about adherence and the implementation of numerous strategies, treatment adherence remains suboptimal for many diseases. Among interventions that have been successful, few have demonstrated clinically meaningful, long-lasting outcomes. This situation highlights the need for a paradigm shift in addressing the problem of adherence.

In considering a new paradigm, some observations may be helpful. The first is that most medication adherence interventions have focused on reducing behavioral burden (eg, strategies to address forgetfulness). Yet experience suggests that multiple factors impact adherence and that emotional, attitudinal, and behavioral factors are important in determining adherence.

The second consideration is that barriers to treatment adherence often differ from one patient to another and, in fact, often change over time in the same patient. The patient may not take a medication for T2DM today because he experienced a hypoglycemic episode yesterday. Tomorrow, he may forget to take his medication because the night before he did not place his medication beside his coffee mug. At the same time, he is not convinced he needs to take medication for a disease (diabetes) that is not causing symptoms.

The inter- and intra-individual factors contributing to poor adherence make it clear that the treatment plan needs to be individualized. In doing so, greater attention needs to be given to the patient’s perspective, with the provider identifying patient concerns and barriers to therapy and collaborating with the patient to find solutions that the patient is willing and able to implement. It is important that this collaborative process is undertaken at each visit, with ongoing support available between visits, if necessary.

Unfortunately, patients and providers are often not “on the same page.” Providers often have difficulty identifying their patients’ concerns and the information and skills their patients need to feel more confident in managing their diabetes. In addition, patients and providers often have different goals regarding long-term medication usage.

Lastly, chronic diseases have become more common and may represent a greater challenge to treatment adherence and overall patient self-management than acute diseases. Yet, chronic diseases are generally approached using an acute-care model. While the acute treatment of a disease often requires days or a few weeks of treatment, a chronic disease requires lifelong treatment. Adhering to medications that require administration once daily or more frequently in perpetuity can be challenging. Therefore, new methods of medication administration are needed to suit the chronicity of the disease.

ADHERENCE: THE PATIENT’S PERSPECTIVE

The health outcomes of a patient with a chronic disease such as T2DM are largely determined by the patient’s self-management of the disease. Collaborative decision-making, which is often accomplished through the use of motivational interviewing strategies, engages patients in the process of making medical decisions through improving knowledge and helping them clarify their values regarding the risks and benefits of each of the available treatment options. Beyond discussing factual information, the process incorporates patient preferences into health decisions. Further information about motivational interviewing can be found at: http://www.motivationalinterviewing.org/.

The key beliefs that influence patients’ values and preferences regarding medications and ultimately adherence can be grouped under 2 orthogonal categories, as has been developed in the Necessity-Concerns Framework: perception of personal need for treatment (necessity beliefs) and concern about the various potential adverse consequences.
of each medication (concerns). A survey of 405 patients with T2DM showed that those with a high level of diabetes-related knowledge and strong belief in the necessity of their diabetes medications demonstrated significantly greater adherence. Conversely, those with a high level of concern about adverse consequences of diabetes medications were less adherent. It has also been suggested that concerns about adverse consequences of glucose-lowering medications may more strongly influence adherence than necessity beliefs. In total, how the patient balances his own necessity beliefs vs medication concerns is a greater determinant of medication adherence than sociodemographic variables (eg, education, gender, age) and clinical variables (type of illness, number of medications).

STRATEGIES TO IMPROVE PATIENT ADHERENCE IN PRIMARY CARE
To facilitate the paradigm shift needed to address the problem of poor adherence, what can be done now in the primary care setting? What systems and advances are on the horizon that might help?

To improve medication adherence, the key is to consider strategies that enhance communication between provider and patient and promote greater understanding of the patient’s perspective. This can be done through application of the Necessity-Concerns Framework as part of a collaborative decision-making process.

Patient responsibility
The first strategy is to recognize that adherence ultimately rests with the patient. As providers, however, we need to collaborate with the patient to identify and address critical barriers to adherence. We cannot solve the problem for the patient, but rather we can work with the patient to find 1 or more solutions that the patient finds acceptable and is willing and able to implement and continue long-term. The following scenarios are real-world strategies to identify and resolve common patient barriers to medication adherence.

Communication
Following are approaches the provider may use during a patient visit to determine patient understanding and actual adherence.

To identify patient understanding of treatment and its importance:

Provider:  • “Please tell me what you know about diabetes and the impact it can have on your health.”
  • “What do you think are the benefits of taking your medications?”
  • “What do you think are the potential negatives about your medications?”

To ascertain actual adherence, the provider should normalize the likelihood of poor adherence; in other words, give the patient “permission” to not be 100% adherent.

Provider:  • “Most patients tell me they find it difficult to take their medications every day as we’ve agreed. How often would you guess that you skip or forget to take your medications?”
  • “Think back to the last time that you didn’t take your medications as we’ve agreed. What was the main reason?”

Emotional distress
Medication adherence can be affected by emotional distress caused by everyday events such as work or family demands. Emotional distress frequently stems from beliefs and demands related to diabetes. Patients often believe that diabetes is ultimately fatal (and therefore, ongoing treatment is pointless) or have heard that medications are commonly associated with negative outcomes such as hypoglycemia, weight gain, and perhaps even cancer.

Provider: “I imagine you have heard many things about diabetes and medications used to treat it. What are some things you have heard that worry you the most?”

Patient: Provides a list

Provider: “Those are interesting, so let’s identify the ones that are most important and work together to come up with a plan to address them. I’d also like to share a secret about diabetes with you. What really matters is that we work together to develop a treatment plan that you feel comfortable about following. If we do that together, the odds are good that you can live a long, healthy life.”

Cost/financial constraints
Cost and affordability are important determinants of adherence to medications, particularly for patients with low income, in poor health, and on multiple medications.

Provider: “With your insurance coverage, are you able to afford the out-of-pocket cost of your medications?”

If No: “Would it be okay if we explore how you might receive your medications at a reduced cost?”

If Yes: “Are you willing to spend the money for the out-of-pocket cost of your medications?” If No: “What would need to happen for you to spend the money for your medications?”

The effect of cost on patient medication adherence is influenced by patient trust in the provider. Patients have been shown to be more likely to forgo medications because of
higher out-of-pocket cost when provider trust level is low. Furthermore, patients with high medical cost burden have significantly greater likelihood of lacking adequate trust in their provider to put the patient’s needs above all else.87

Advances in medications
A variety of approaches are available to address the burden-some and often complex nature of chronic medication use. Among the most commonly used is a fixed-dose combination of 2 glucose-lowering medications, 1 of which is usually metformin. Premixed insulins consisting of a basal and a bolus insulin have been available for decades, while fixed-ratio combinations of basal insulin and a glucagon-like peptide-1 receptor agonist (GLP-1RA) were approved in 2016. Adherence with a fixed-dose combination product is somewhat less than with monotherapy but greater than with dual therapy with the individual medications.88-91 Medications with a long duration of action and flexible dosing times have also been developed. These include the GLP-1RAs albiglutide, dulaglutide, exenatide once-weekly, and lixisenatide-1 receptor agonist (GLP-1RA) were approved in 2016. Adherence with a fixed-dose combination product is somewhat less than with monotherapy but greater than with dual therapy with the individual medications.88-91 Among the advances in delivery systems has been the evolution from vials and syringes to sophisticated pen devices for injecting insulin and GLP-1RAs. In addition to being more easily carried, pre-filled cartridges make it easy to load medication into the device. Accurate dosing is facilitated via various dose selectors with easy-to-read display and audible features. Ultra-fine needles minimize injection pain. These features have been shown in numerous studies to improve patient satisfaction and adherence compared with vials and syringes.34-37,101

Advances in delivery systems
Pen devices
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Insulin pumps
Another advance in the administration of insulin in patients with type 1 diabetes mellitus (T1DM) and, more recently, T2DM is the use of insulin pump therapy. More than a decade ago, DeVries et al showed that continuous, subcutaneous insulin infusion improves glycemic control and some aspects of health-related quality of life in patients with T1DM and a history of long-term, poor glycemic control.102 Recently, positive changes in overall well-being, perceived control over diabetes, hypoglycemic safety, and diabetes distress have been reported by patients with T2DM using a continuous, subcutaneous insulin infusion system.103 These results are likely related to fewer missed doses with insulin pump therapy.

Osmotic mini-pump
Under FDA review is an implantable osmotic mini-pump that delivers a continuous subcutaneous release of the GLP-1RA exenatide at a predetermined rate for up to 6 months, obviating the need for twice-daily or once-weekly injection. The match stick-sized osmotic mini-pump is aseptically placed in the abdominal region during a brief office procedure (FIGURE).104 The ITCA 650 mini-pump ensures a consistent therapeutic level for up to 6 months.105 Because ITCA 650 is placed subcutaneously, 100% adherence seems likely.

The efficacy and safety of ITCA 650 have been demonstrated in phase 3 trials. In the FREEDOM-1 trial, patients inadequately controlled with diet and exercise or oral medications (N=460) were randomized to ITCA 650 at 40 µg/d or 60 µg/d (20 µg/d for the first 13 weeks for both) or placebo for 39 weeks.106 From a mean baseline of 8.5%, placebo-subtracted HbA1c reductions were 1.1% and 1.2% for the 40 µg/d and 60 µg/d doses, respectively. The FREEDOM-2 trial randomized 535 patients on metformin ≥1500 mg/d 60 µg/d (20 µg/d for the first 13 weeks for both) or placebo for 39 weeks.106 From a mean baseline of 8.5%, placebo-subtracted HbA1c reductions were 1.1% and 1.2% for the 40 µg/d and 60 µg/d doses, respectively. The FREEDOM-2 trial randomized 535 patients on metformin ≥1500 mg/d or placebo, and the difference in HbA1c between the ITCA 650 and placebo groups at 39 weeks was 1.0% and 0.8%, respectively. Body weight decreased 4.0 kg vs 1.3 kg, respectively. Minor hypoglycemia occurred in 4.2% of patients on ITCA 650 and 1.9% of those on sitagliptin. Gastrointestinal adverse events were more common with ITCA 650 and were mostly transient.

CALL TO ACTION
Poor medication adherence continues to have a major negative impact on health outcomes in patients with diabetes mellitus. It is time that this reality is recognized and that a paradigm shift occurs in clinical practice, with steps taken in primary care to minimize the chance for poor medication adherence.
adherence when developing the treatment plan. Among the numerous strategies that have been explored and recommended are improved provider-patient communication that integrates the Necessity-Concerns Framework and use of medications and delivery systems designed to improve adherence. The adoption of new delivery systems and other technology-based solutions as they become available may further improve medication adherence.

REFERENCES
5. Viertel JJ, Wladarczyk CS, Lorenz R, et al. Missed doses of oral antihyperglycemic medications and delivery systems designed to improve adherence when developing the treatment plan. Among the numerous strategies that have been explored and recommended are improved provider-patient communication that integrates the Necessity-Concerns Framework and use of medications and delivery systems designed to improve adherence. The adoption of new delivery systems and other technology-based solutions as they become available may further improve medication adherence.


The Cardiovascular Safety of Nonsteroidal Anti-Inflammatory Drugs: Putting the Evidence in Perspective

Martin Quan, MD

INTRODUCTION
Pain and inflammation are common complaints experienced by all humans at some time during their lifetime. Among the wide variety of available analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for relief of acute and chronic pain. Data from the 2010 National Health Interview Survey suggest that approximately 43 million adults in the United States took aspirin at least 3 times per week for more than 3 months, while more than 29 million adults used an NSAID regularly.1 Traditional NSAIDs (tNSAIDs), such as aspirin, ibuprofen, naproxen, and diclofenac, represent an effective, long-lasting option that may offer advantages over cyclooxygenase-2 (COX-2) selective NSAIDs, such as celecoxib. The use of NSAIDs is not without controversy, however.

The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, published in 2000, was the first to raise concerns that NSAIDs (specifically, the COX-2 selective inhibitor rofecoxib) might be associated with a higher risk for cardiovascular (CV) events.2 As discussed below, subsequent trials and meta-analyses have demonstrated a higher CV risk with use of not only COX-2 inhibitors (coxibs) but also certain tNSAIDs. These investigations have contributed to actions by the US Food and Drug Administration (FDA), most recently in July 2015, requiring strengthening of CV risk warnings on labels for all prescription and over-the-counter NSAIDs, despite evidence suggesting that differences in CV risk may exist among the NSAIDs.

To address unanswered questions regarding CV risk of coxibs vs tNSAIDs, the FDA mandated a comparison of celecoxib with 2 tNSAIDs, ibuprofen and naproxen.3 As a result, the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial was launched in 2006. PRECISION was a noninferiority trial to assess CV outcomes with long-term use, with secondary end points such as gastrointestinal (GI), renal, and other outcomes. The results of the PRECISION trial, published in November 2016, are difficult to interpret because of the study’s limitations and may have contributed to confusion regarding the CV safety of NSAIDs. Before further discussing the PRECISION trial and its implications for primary care providers, it is important to put the PRECISION trial in perspective by highlighting the pharmacologic differences among the NSAIDs and their implications for CV safety and considering a historical review of key CV safety trials involving NSAIDs.

CLINICAL PHARMACOLOGY OF NSAIDs
NSAIDs reduce pain and inflammation through inhibition of the cyclooxygenase enzyme, resulting in downstream inhibition of the production of thromboxane A2 (TxA2), prostacyclin, and other prostanoids.4 The analgesic and anti-inflammatory effects of NSAIDs largely result from inhibition of the COX-2 isoform at sites of inflammation, while gastrointestinal and other adverse events stem from inhibition of COX-1 isoforms, which are constitutive, present in most organs, and primarily serve a homeostatic function. For example, in the stomach, COX-1 mediates a cytoprotective effect, helping maintain mucosal integrity by increasing mucosal blood flow and increasing GI mucus and bicarbonate secretion.4,5 Inhibition of COX-1 is the mechanism primarily responsible for the gastric and duodenal ulceration and bleeding long associated with tNSAID use.

In vascular endothelium, COX-2 is involved in the production of prostacyclin (PGI2), which antagonizes platelet activation and produces vasodilation, whereas in platelets, COX-1 is responsible for the production of TxA2, which causes platelet activation and vasoconstriction. It is thought that the selective inhibition of COX-2 by coxibs results in a relative reduction in endothelial PGI2 synthesis, leaving platelet production of TxA2 intact. As a result, it has been theorized that coxibs shift the balance of prostaglandin...
production to TxA₂ at the platelet-vascular endothelial interface, thereby favoring thrombogenic stimulation and arterial vasoconstriction and a greater risk for an atherothrombotic cardiovascular event.6

Although COX-2 selectivity is a likely contributor to the higher CV risk seen with NSAID use, it is not the only factor, given that a higher CV risk has been seen with both coxibs as well as tNSAIDs. Other important variables implicated in NSAID risk include dosage, half-life, impact on blood pressure, and interaction with aspirin.7

**ASPIRIN INTERACTION**

In contrast to inhibition of arachidonic acid observed with other NSAIDs, aspirin causes an irreversible inactivation of COX-1 and COX-2. Inhibition of COX-1 is responsible for the antiplatelet effects of aspirin and its cardioprotective effect.4

The coadministration of some tNSAIDs, eg, ibuprofen and naproxen (but not COX-2 selective inhibitors), with low-dose aspirin (LD-ASA) causes transient and modest inhibition of COX-1 and has been shown to interfere with the antiplatelet effect of aspirin.7,8 The effect of naproxen on the antiplatelet effect of LD-ASA may be lower than with ibuprofen.9 Concerns that such an interaction might reduce the cardioprotective effect of LD-ASA resulted in an advisory from the FDA in 2007 recommending ibuprofen be taken at least 30 minutes after aspirin to avoid any potential interaction.10 Taking naproxen 2 hours after aspirin appears to lessen the interference.11 Furthermore, there is evidence that suggests that high-dose naproxen at a prescription dose of 500 mg twice daily may actually produce its own aspirin-like antiplatelet effect.12

The variable effect of NSAIDs to interfere with the ability of aspirin to inhibit platelet activation may be due to differences in their ability to form hydrogen bonds with specific amino acids within the COX-1 hydrophobic channel.13 The possibility of differences among NSAIDs with respect to an interaction with aspirin is of clinical importance as many patients who use NSAIDs for anti-inflammatory and analgesic effects often use LD-ASA to prevent CV events. This becomes a particularly important consideration in older adults with osteoarthritic pain, who are likely to be at increased CV risk.14

**CARDIOVASCULAR SAFETY**

The CV safety of NSAIDs has been assessed in hundreds of clinical trials over the past almost 2 decades. Details regarding several key clinical trials are provided in the **TABLE**.2,15-22 These trials show that NSAIDs variably alter the rate of thromboembolic events and suggest that NSAIDs with a greater affinity for COX-2, particularly at higher doses, are associated with a higher CV risk.

**KEY PROSPECTIVE CLINICAL TRIALS**

The VIGOR trial was the first trial to suggest a higher incidence of adverse CV outcomes with COX-2 selective inhibitors compared with tNSAIDs.2 After a median follow-up of 9 months, the incidence of myocardial infarction (MI) was found to be 4-fold higher with rofecoxib than naproxen (0.4% vs 0.1%, respectively).2 A post hoc analysis was also concerning, showing that the relative risk for developing a confirmed, adjudicated thrombotic CV event with rofecoxib compared with naproxen was 2.38 (95% confidence interval [CI], 1.39–4.00).15

The Adenoma Prevention with Celecoxib (APC) trial compared 2 doses of celecoxib (200 mg or 400 mg twice daily) with placebo for the prevention of colorectal adenomas.16 After approximately 3 years of follow-up, the study was terminated early because of a dose-related increase in a composite of CV events with celecoxib.

The Adenomatous Polyp Prevention on Vioxx (APPROVe) trial determined the effect of rofecoxib vs placebo on the risk for recurrent neoplastic polyps of the large bowel in patients with a history of colorectal adenomas.17 The rate of a confirmed thrombotic event was significantly higher with rofecoxib, becoming apparent after 18 months of treatment. The results primarily reflect a greater number of MIs and ischemic cerebrovascular events in the rofecoxib group. The results of the APPROVe trial contributed to the withdrawal of rofecoxib from the market in 2004.

The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) assessed the CV outcomes in high-risk patients with osteoarthritis. TARGET comprised 2 parallel substudies comparing the COX-2 selective inhibitor lumiracoxib (not available in the United States) 400 mg daily with either ibuprofen 800 mg three times daily or naproxen 500 mg twice daily.18 In aspirin users, ibuprofen was associated with a significantly higher rate of CV events at 1 year compared with lumiracoxib, whereas naproxen was not. In nonaspirin users, naproxen was associated with significantly fewer CV events compared with lumiracoxib, whereas ibuprofen was not. In addition, ibuprofen was associated with a higher rate of congestive heart failure. Shortcomings of this trial included the post hoc design; not being appropriately powered for CV safety, resulting in imprecision due to the small number of events in the subgroups; the use of aspirin in some but not all patients for unspecified reasons; lack of data collection on aspirin use during the study; and a lack of a placebo arm, making it difficult to evaluate absolute CV risk.

The Alzheimer’s Disease Anti-Inflammatory Prevention Trial (ADAPT) evaluated naproxen 220 mg twice daily and celecoxib 200 mg twice daily with placebo for the primary prevention of Alzheimer’s dementia.19 After the results of the APC trial were released, the ADAPT study was terminated,
TABLE  Evidence concerning the cardiovascular risks associated with COX-2 inhibitors

<table>
<thead>
<tr>
<th>Trial; year(s) conducted</th>
<th>Design; patients</th>
<th>Treatment</th>
<th>Results&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Limitations</th>
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<tr>
<td><strong>VIGOR, 1999&lt;sup&gt;15&lt;/sup&gt;</strong></td>
<td>R, DB, MC Patients with RA (N=8076)</td>
<td>Rofecoxib 50 mg/d vs Naproxen 500 mg bid (median follow-up 9 mos)</td>
<td>Gi events (per 100 PY): 2.1 vs 4.5 (HR, 0.5; 95% CI, 0.3-0.6) MI: 0.4% vs 0.1% MACE&lt;sup&gt;b&lt;/sup&gt;: HR, 2.38; 95% CI, 1.39-4.00</td>
<td>Withdrawal from treatment: 29.3% vs 28.5%; not placebo-controlled</td>
</tr>
<tr>
<td><strong>APC, 1999-2002&lt;sup&gt;16&lt;/sup&gt;</strong></td>
<td>R, DB, MC Patients at risk for colorectal adenoma (N=2035)</td>
<td>Celecoxib 200 mg bid vs Celecoxib 400 mg bid vs Placebo (2.8-3.1 y follow-up)</td>
<td>MACE&lt;sup&gt;c&lt;/sup&gt;: HR vs PBO: HR, 2.3; 95% CI, 0.9-5.5; HR, 3.4; 95% CI, 1.4-7.8</td>
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<td><strong>APPROVe, 2000-2001&lt;sup&gt;17&lt;/sup&gt;</strong></td>
<td>R, DB, MC Patients with colorectal adenoma (N=2586)</td>
<td>Rofecoxib 25 mg/d vs Placebo X 3 y</td>
<td>Thrombotic event&lt;sup&gt;d&lt;/sup&gt; (per 100 PY): 1.50 vs 0.78 (HR, 1.92; 95% CI, 1.19-3.11) Cardiac events (per 100 PY): 1.01 vs 0.36 (HR, 2.80; 95% CI, 1.44-5.45) Cerebrovascular events (per 100 PY): 0.49 vs 0.21 (HR, 2.32; 95% CI, 0.89-6.74)</td>
<td>Withdrawal from treatment: 31.9% vs 24.6%</td>
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<tr>
<td><strong>TARGET, 2001-2002&lt;sup&gt;18&lt;/sup&gt;</strong></td>
<td>R, DB, MC Patients with OA ages ≥50 y (N=18,325)</td>
<td>Lumiracoxib 400 mg/d vs Ibuprofen 800 mg tid X 52 wks</td>
<td>High-risk using aspirin (75-100 mg/d): MACE&lt;sup&gt;e&lt;/sup&gt;: 0.25% vs 2.14% (HR, 9.08; 95% CI, 1.13-72.8) High-risk not using aspirin: MACE&lt;sup&gt;e&lt;/sup&gt;: 0.80% vs 0.92% (HR, 0.91; 95% CI, 0.15-5.47)</td>
<td>Post hoc analysis; not placebo-controlled; few events; withdrawal from treatment: 43%</td>
</tr>
<tr>
<td><strong>ADAPT, 2001-2004&lt;sup&gt;19&lt;/sup&gt;</strong></td>
<td>R, DB, MC Patients ages ≥70 y with family history of AD (N=2528)</td>
<td>Celecoxib 200 mg bid vs Naproxen 220 mg bid vs Placebo X 3 y</td>
<td>MACE&lt;sup&gt;f&lt;/sup&gt;: 5.54% vs 8.25% vs 5.68% [HR vs PBO: HR, 1.10; 95% CI, 0.67-1.79; HR, 1.63; 95% CI, 1.04-2.55]</td>
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with a median of approximately 15 months of treatment. ADAPT findings suggested the cardiovascular and cerebrovascular risks with celecoxib were similar to placebo. The CV risk was significantly greater with naproxen compared with placebo, due to a higher incidence of heart failure and transient ischemic attack. Besides early termination, the study had several limitations, including that it was not designed to detect differences in CV or cerebrovascular risk and was not appropriately powered for CV safety, resulting in imprecision due to the small number of events; the patient population had unknown CV risk at baseline, complicating extrapolation to the general population; and there was no a priori procedure for adjudication of CV or cerebrovascular events.

Lastly, the Standard care versus Celecoxib Outcome Trial (SCOT) was a prospective, open, blinded end point trial that compared the CV and GI safety of celecoxib with a variety of tNSAIDs (eg, diclofenac, ibuprofen, naproxen, meloxicam) in patients ages >60 years with osteoarthritis (OA) or rheumatoid arthritis (RA) but free of CV disease. Over a median of 3 years, fewer patients than expected developed an on-treatment CV event with a rate similar for celecoxib and tNSAIDs. Although the trial was conducted in the United Kingdom, Denmark, and the Netherlands, full data regarding mean NSAID daily doses were available only in Scotland: celecoxib 169.8 mg (standard deviation [SD], 80.6), diclofenac 79.4 mg (SD, 38.3), ibuprofen 675.9 mg (SD, 345.9), and...
naproxen 581.9 mg (SD, 263.4). Significantly more patients withdrew from celecoxib than tNSAIDs, with the dominant reason being lack of efficacy. The rate of NSAID-associated GI complications was low (attributed by the authors to the coadministration of concomitant anti-ulcer agents as well as the relatively low doses of the NSAIDs used; as expected, the rate was higher with tNSAIDs than with celecoxib.

**TABLE** Evidence concerning the cardiovascular risks associated with COX-2 inhibitors (Continued)

<table>
<thead>
<tr>
<th>Trial; year(s) conducted</th>
<th>Design; patients</th>
<th>Treatment</th>
<th>Results*</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danish Registry, 1997-200622</td>
<td>Retrospective review of national registry; Patients ages ≥30 y with first-time MI (N=83,675)</td>
<td>Any NSAID</td>
<td>Risk for death or recurrent MI (&gt;90 days treatment) All NSAIDs: HR, 1.55; 95% CI, 1.46-1.64 Rofecoxib: HR, 1.72; 95% CI, 1.45-2.04 Celecoxib: HR, 1.65; 95% CI, 1.42-1.92 Ibuprofen: HR, 1.53; 95% CI, 1.40-1.69 Diclofenac: HR, 1.92; 95% CI, 1.66-2.22 Naproxen: HR, 1.50; 95% CI, 0.10-2.05 Other NSAIDs: HR, 1.44; 95% CI, 1.28-1.62</td>
<td>Observational design; informational bias</td>
</tr>
<tr>
<td>SCOT, 2008-201320,21</td>
<td>PROBE, MC; Patients ages ≥60 y with OA or RA (N=7297)</td>
<td>Celecoxib ≤200 mg bid vs tNSAID† (median follow-up 3 y)</td>
<td>MACE (per 100 PY): 1.14 vs 1.10 (HR, 1.04; 95% CI, 0.81-1.33) Hospitalization or death for upper GI ulcer (per 100 PY): 0.09 vs 0.04 (HR, 2.08; 95% CI, 0.65-7.74)</td>
<td>Withdrawal from treatment: 48.2% vs 31.5%</td>
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</table>

Abbreviations: AD, Alzheimer’s disease; ADAPT, Alzheimer’s Disease Anti-inflammatory Prevention Trial; APC, Adenoma Prevention with Celecoxib; APPROVe, Adenomatous Polyp Prevention on Vioxx; bid, twice daily; CHF, congestive heart failure; CV, cardiovascular; d, day; DB, double-blind; GI, gastrointestinal; HR, hazard ratio; MACE, major adverse cardiovascular events; MC, multicenter; MI, myocardial infarction; N/A, not applicable; N, number; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PBO, placebo; PROBE, prospective, randomized, open-label, blinded endpoint evaluation; PY, person-years; R, randomized; RA, rheumatoid arthritis; SCOT, Standard care versus Celecoxib Outcome Trial; TARGET, Therapeutic Arthritis Research and Gastrointestinal Event Trial; tid, 3 times daily; tNSAID, traditional, ie, non-COX-2 selective NSAID; VIGOR, Vioxx Gastrointestinal Outcomes Research; wks, weeks; y, year(s).

*95% confidence interval.
†Composite of MI, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, transient ischemic attack.
‡Composite of CV death, MI, stroke, heart failure.
§Composite of fatal and nonfatal MI, unstable angina, sudden cardiac death, fatal and nonfatal ischemic stroke, transient ischemic attack, peripheral arterial thrombosis, peripheral venous thrombosis, pulmonary embolism.
¶Composite of CV death, nonfatal MI, stroke.
**Composite of CV death, MI, stroke, congestive heart failure, transient ischemic attack.
††Ibuprofen, acetylsalicylic acid, aspirin, dexamethasone, diclofenac sodium, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tiaprofenic acid, diclofenac/misoprostol.
‡‡Composite of hospitalization for nonfatal MI or other biomarker for positive acute coronary syndrome, nonfatal stroke, or CV death.

**DANISH REGISTRY STUDY**

A nationwide registry of Danish patients ages ≥30 years admitted with first-time MI was analyzed to assess NSAID use and CV risk. Overall, NSAID treatment was significantly associated with an increased risk for death/recurrent MI commencing within 7 days of treatment initiation (hazard ratio [HR], 1.45; 95% CI, 1.29-1.62).22 The risks persisted over more than 5 years of follow-up, with an increased risk for death (HR, 1.60; 95% CI, 1.49-1.71) and coronary death or nonfatal recurrent MI (HR, 1.14; 95% CI, 1.29-1.56).23 The risk for coronary death or nonfatal recurrent MI was greater with rofecoxib (HR, 2.19; 95% CI, 1.27-3.77) than with celecoxib (HR, 1.17; 95% CI, 0.63-2.17). Among the most commonly used tNSAIDs, the risk was greatest with diclofenac (HR, 1.58; 95% CI, 1.31-1.91) and lowest with naproxen (HR, 1.15; 95% CI, 0.71-1.85).

The bleeding rates were also significantly greater in patients treated with NSAID therapy. The risk for a CV event or bleeding was independent of concomitant antithrombotic treatment.24 These results suggest that NSAIDs should be used cautiously, if at all, in patients with a history of MI.

**META-ANALYSES**

Meta-analyses have been conducted to assess the CV risk of NSAIDs. The McGgettigan-Henry meta-analysis examined population-based controlled observational studies of individual NSAIDs used at typical doses in community settings.25 Trelle et al conducted a network meta-analysis of 31 large-scale, randomized controlled trials comparing any NSAID with another NSAID or placebo.26 The Coxib and Traditional NSAID Trialists’ (CoxIT) Collaboration identified 639 randomized
The 3 meta-analyses yielded generally similar results, suggesting that all NSAIDs are associated with an increased CV risk, with naproxen conferring the lowest risk. The CNT analysis showed the estimated relative risk for major CV events among the tNSAIDs vs placebo was highest with diclofenac (HR, 1.41; 95% CI, 1.12-1.78) and lowest with naproxen (HR, 0.93; 95% CI, 0.69-1.27).27 Although the CNT analysis demonstrated a similar risk for major CV events with rofecoxib and celecoxib, the McGettigan-Henry analysis showed a higher risk with rofecoxib (HR, 1.45; 95% CI, 1.33-1.59) vs celecoxib (HR, 1.17; 95% CI, 1.08-1.27).27 All 3 meta-analyses provided support to the premise that the CV risk associated with celecoxib was dose-dependent, with the CNT and the McGettigan-Henry analyses suggesting no increased risk with doses of 200 mg daily. In addition to looking at CV risk, the CNT analysis also examined upper GI complications (ie, upper GI bleeding and/or perforation, or peptic ulcer) and showed the risk to be nearly twice as high for ibuprofen and naproxen compared with diclofenac or a coxib.27

US FOOD AND DRUG ADMINISTRATION ACTIONS

Following publication of the CNT meta-analysis, the FDA convened 2 advisory panels to review this and other related information.28 Results of this meeting, as well as its own analysis, led the FDA to issue a drug safety communication in July 2015 that required prescription NSAID labels to communicate the following:

• The risk for heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.

• The risk appears greater at higher doses.

• It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.

• NSAIDs can increase the risk for heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.

• In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke follow-

ing NSAID use than patients without these risk factors because they have a higher risk at baseline.

• Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared with patients who were not treated with NSAIDs after their first heart attack.

• There is an increased risk for heart failure with NSAID use.

PRECISION TRIAL

This CV safety trial mandated by the FDA in 2014 was initiated in 2006 following a 2004 FDA review. The PRECISION trial enrolled patients who required NSAID therapy for OA or RA and were deemed at high CV risk for CV disease based on having established CV disease or risk factors for CV disease (approximately 35% of patients had a history of diabetes, 78% a history of hypertension, and 62% a history of dyslipidemia). Patients were randomized to celecoxib 100 to 200 mg twice daily, ibuprofen 600 to 800 mg three times daily, or naproxen 375 to 500 mg twice daily. The primary endpoint was noninferiority on the composite of CV death (including hemorrhagic death), nonfatal MI, or nonfatal stroke. A total of 24,081 patients were randomized with a mean treatment duration of 20.3 months and a mean follow-up period of 34.1 months. During the trial, 68.8% of patients stopped taking the treatment drug and 27.4% discontinued follow-up.

Celecoxib was found to be noninferior to ibuprofen and naproxen with regard to CV safety, with the primary endpoint occurring in 2.3% of celecoxib patients compared with 2.7% and 2.5% of ibuprofen and naproxen patients, respectively.3 Hazard ratios for celecoxib were 0.85 (95% CI, 0.70-1.04) vs ibuprofen and 0.93 (95% CI, 0.76-1.13) vs naproxen (P<.001 for both). In contrast, pairwise comparisons for each of the components of the primary endpoint showed no significant differences between celecoxib and ibuprofen as well as celecoxib and naproxen. As expected, based on their mechanistic differences, the risk for GI events was significantly lower with celecoxib than with ibuprofen (P=.002) or naproxen (P=.01). The risk for renal events was significantly lower with celecoxib compared with ibuprofen (P=.004) but not compared with naproxen (P=.19).

The design and results of PRECISION have been questioned and its findings should be interpreted with caution.29 In addition to high rates of patients discontinuing the study drug as well as discontinuing follow-up, the rate of primary outcome events occurring during the study period was considerably lower than expected and appeared more indicative of a study group at relatively low risk for CV events. Because of this lower rate and problems with subject recruitment, the statistical power for noninferiority, which was originally planned to be 90%, was relaxed to 80%, thereby lessening the reliability of any judgment of noninferiority. Moreover, based
on prior studies, the CV risk associated with celecoxib use appears dose-related. In the PRECISION trial, the mean daily celecoxib dose of 209 mg may be considered low dose and lower than that associated with increased CV risk. For comparison, the mean daily doses of ibuprofen and naproxen were 2045 mg and 852 mg, respectively. Lastly, since interference with the antiplatelet activity of LD-ASA and potential negation of its cardioprotective effect is not a class effect (ie, both naproxen and ibuprofen have been shown to interfere with the antiplatelet activity of aspirin, whereas celecoxib has not), the failure to control for use of LD-ASA use introduces a potential source of bias favoring celecoxib and calls into question any conclusions in this regard.

SUMMARY
At the present time, the totality of evidence suggests that all NSAIDs are associated with an increased risk for adverse CV events. Several factors are involved, including COX-2 selectivity, dosage, half-life, impact on blood pressure, and interaction with aspirin. Although the evidentiary standard needed by the FDA to rank order NSAID compounds with regard to CV risk has not been met, the balance of evidence continues to favor naproxen as the safest NSAID from a CV perspective. A caveat is that naproxen may also pose a higher risk for an upper GI bleed than other tNSAIDs. Although data from the SCOT trial and the PRECISION trial support the improved CV safety of low-dose celecoxib (200 mg daily) seen in earlier studies, the shortcomings of these 2 trials serve only to raise doubt regarding any conclusions about the comparative safety of the NSAID agents studied and leaves unanswered the question of differential CV risk.

Although widely used and clinically valuable, NSAID use is not without risk. When considering the use of an NSAID, careful consideration of risk factors associated with NSAID toxicity should be given, including the patient’s age and the risk for developing renal, GI, and CV complications. NSAIDs should be used only with due caution in patients with known CV disease and are best avoided in patients following an MI. Until definitive evidence becomes available, it remains prudent to follow the basic rule of prescribing the lowest effective dose of an NSAID for the shortest duration possible.

REFERENCES
Sublingual Immunotherapy: A Guide for Primary Care

Eli O. Meltzer, MD

INTRODUCTION

Allergen immunotherapy (AIT), the only potential disease-modifying treatment for allergic disease, has been used for more than a century.1 Hankin et al showed significant reduction in pharmacy, outpatient, and inpatient resources in the 6 months following vs the 6 months preceding AIT in Medicaid-enrolled children with allergic rhinitis (AR).2 A 2013 analysis showed sustained cost reduction over 18 months in patients with AR treated with AIT compared with matched control subjects not treated with AIT.3 The overall cost savings were 38% with AIT, which was similar to the cost savings observed in adults.

AIT is underused, partly because of the lack of familiarity of nonallergy/immunology-trained health care providers, and partly because of safety concerns (primarily anaphylaxis risk) associated with its subcutaneous administration.1 These safety concerns, as well as practical and logistic considerations associated with administration of subcutaneous immunotherapy (SCIT), spurred interest in the use of sublingual immunotherapy (SLIT), which can be self-administered, does not require injections, and carries a much lower risk of anaphylaxis compared with SCIT.4 While SLIT has been used outside the United States for decades, the US Food and Drug Administration (FDA) has recently approved 4 SLIT allergen extract products (tablets) for treatment of the symptoms and morbidity associated with grass pollen, ragweed, or house dust mite AR, with or without conjunctivitis.

Grass and ragweed allergens are among the most common aeroallergens and characteristically cause seasonal allergic rhinoconjunctivitis (ARC) and/or seasonal allergic asthma. On the other hand, cat dander, cockroach, or dust mite allergens cause symptoms year-round and are associated with perennial AR and/or allergic asthma.4

Medical management of seasonal and perennial nasal allergic disease typically involves allergen avoidance and use of pharmacotherapeutic agents such as nonsedating oral antihistamines, intranasal antihistamines, intranasal cromolyn and, most importantly, intranasal corticosteroids.5 Required daily use for efficacy raises concerns regarding long-term adherence, safety, and cost. Allergic asthma control with long-term use of inhaled steroids and long-acting bronchodilators also poses risks.4

Since allergic disease is an immunologic, systemic disorder with local manifestations, it is not surprising that treatment with immunotherapy can modify the underlying natural history of the disease, resulting in long-term efficacy (ie, immune tolerance) after termination of treatment.6,7 Unlike pharmacotherapy, AIT can also reduce the incidence of subsequent asthma in patients with AR and reduce sensitization to new allergens.8

AIT is most beneficial for patients with moderate-to-severe intermittent or persistent symptoms of AR or ARC, particularly those whose symptoms are not responsive to pharmacotherapy and environmental control measures.1

Mechanisms of SCIT and SLIT

Whether by the subcutaneous or sublingual route, administration of AIT leads to very early decrease in susceptibility of mast cells and basophils to degranulation (ie, rapid desensitization), possibly due to upregulation of histamine type 2 receptors and decreased effector cell function.9 This is followed by generation of allergen-specific regulatory T cells and suppression of allergen-specific Th1 and Th2 cells, and, after several months, a significant decrease in the allergen-specific IgE/IgG4 ratio and a decrease in tissue mast cell and eosinophil numbers and release of mediators.6

Allergen extracts administered sublingually are taken up by dendritic cells in the oral mucosa and presented to T cells in the draining lymph nodes, likely resulting in activation of regulatory T cells and downregulation of mucosal mast cells.10 The low level of effector cells such as mast cells, basophils, and eosinophils within the oral and sublingual mucosa...
is believed to be an important factor in the lower rates of adverse systemic allergic reactions observed with SLIT compared with SCIT.\textsuperscript{10}

**Subcutaneous immunotherapy**

SCIT has been shown to be highly effective in reducing both symptoms and use of medications in patients with seasonal AR and ARC with or without asthma.\textsuperscript{4,11} However, subcutaneous administration can be associated with systemic allergic reactions, including, rarely, anaphylaxis and death.\textsuperscript{1,5} Therefore, SCIT must be administered in a setting with immediate access to resuscitative measures.

The discomfort of injections and inconvenience of office visits for SCIT also contribute to underuse of SCIT as a therapeutic option and to low adherence among patients.\textsuperscript{1,12} A 2014 survey of patients’ experience with AIT showed that, among patients treated with SCIT (n=456) or SLIT (n=34), only 61.8% and 52.9%, respectively, completed the recommended number of doses.\textsuperscript{12} Although it might have been expected that adherence with SLIT would be higher than with SCIT because of the convenience of treatment at home, personal experience shows that adherence with SLIT also declines over time, as is generally the case with medication adherence. This indicates the importance of supporting patient self-management at each visit.

**Sublingual immunotherapy**

**Overview of available products**

In 2014, the FDA approved 3 sublingual tablets, 1 containing 5 grass pollen extracts (Oralair) and another containing 1 grass (Timothy) pollen extract (Grastek). The third product (Ragwitek) contains a short ragweed pollen extract. Oralair is indicated for the treatment of grass pollen-induced AR with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the 5 grass species contained in the product: Sweet Vernal grass, orchardgrass, perennial ryegrass, Timothy, and Kentucky bluegrass. In contrast, Grastek is limited to treatment of people with positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens.\textsuperscript{13,14} There is low cross-allergenicity among the 5 grass species in the 5-grass pollen product and several of the southern grasses (particularly Bermuda grass).

The short ragweed pollen product Ragwitek is indicated for the treatment of short ragweed pollen-induced AR, with or without conjunctivitis, confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for short ragweed pollen.\textsuperscript{15} A fourth SLIT product (Odactra) was approved by the FDA in March 2017 for house dust mite-induced AR, with or without conjunctivitis.\textsuperscript{16} Several studies indicate that it improves AR in patients with AR and asthma symptoms, with efficacy that is maintained during treatment-free follow-up.\textsuperscript{17,20}

The approved minimum age for use is 5, 10, 18, and 18 years of age, respectively, for Grastek, Oralair, Ragwitek, and Odactra.\textsuperscript{13-16} All are approved for use in adults through 65 years of age.

**Efficacy and impact on natural history of allergy**

For AR, rhinoconjunctivitis, and asthma, numerous double-blind, placebo-controlled trials, as well as several meta-analyses and systematic reviews, have confirmed that SLIT is effective in reducing symptom scores and medication use, improving quality of life, inducing favorable changes in specific immunologic markers, and modifying the course of the condition over time (\textbf{TABLe 1}).\textsuperscript{21-30} Several randomized, double-blind studies demonstrated that 3 years of continuous treatment with the 1- or 5-grass pollen SLIT products resulted in clinical and immunologic benefits that were sustained for at least 2 subsequent years.\textsuperscript{18,19}

The efficacy of SLIT has been compared to either pharmacotherapy or SCIT for management of ARC. A pooled analysis indirectly compared the treatment effect of SLIT (N=3094 in Timothy grass SLIT tablet trials; N=58 in ragweed SLIT tablet trials) vs pharmacotherapies (montelukast, N=6799; desloratadine, N=445; or mometasone furoate nasal spray, N=2140) for seasonal and perennial AR.\textsuperscript{31} Improvement in total nasal symptom scores (TNSSs) relative to placebo in seasonal AR was numerically greater with SLIT than with montelukast and desloratadine (16.3% and 17.1% in the Timothy grass and ragweed trials, respectively, vs 5.4% and 8.5% in the montelukast and desloratadine trials, respectively), and was nearly as great as with mometasone furoate nasal spray (22.2%). Similar outcomes were reported in a meta-analysis indirectly comparing results from 28 pharmacotherapy trials and 10 grass pollen SLIT trials (total number of patients, N=21,223).\textsuperscript{32} Grass pollen SLIT tablets had a greater mean relative clinical impact (based on reported posttreatment or season-long nasal or total symptom score) than second-generation antihistamines and montelukast, and the same mean relative clinical impact as nasal corticosteroids.\textsuperscript{32}

Comparing the efficacy of SCIT with SLIT is difficult because of heterogeneity of allergen composition, dose, duration, and patient selection, particularly among older studies.\textsuperscript{8,33-38} A 2015 network meta-analysis of 37 studies comparing grass pollen SCIT and SLIT tablets demonstrated comparable reduction in ARC symptoms and supplemental medication use during the first pollen season.\textsuperscript{38}
<table>
<thead>
<tr>
<th>Study</th>
<th>Age range (y)</th>
<th>A/P</th>
<th>Dropouts (A/P)</th>
<th>Product tested</th>
<th>Duration</th>
<th>Disease</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durham, 2006&lt;sup&gt;21&lt;/sup&gt;</td>
<td>18-65</td>
<td>569/286</td>
<td>44/21</td>
<td>TGP</td>
<td>8 wks before and during grass pollen season</td>
<td>Grass pollen–induced RCA</td>
<td>Reduction in RC score for symptoms (16%) and medication use (28%) vs placebo ($P_{=.0710}$, $P_{=.0470}$). Better RC QOL scores (17%, $P_{=.006}$) and increased number of well days (18%, $P_{=.041}$). One drug-related serious adverse event (uvular edema); did not require treatment and did not lead to withdrawal. No life-threatening systemic reactions or deaths.</td>
</tr>
<tr>
<td>Nelson 2011&lt;sup&gt;22&lt;/sup&gt;</td>
<td>18-65</td>
<td>213/225</td>
<td>38/33</td>
<td>TGP</td>
<td>16 wks before and during grass pollen season</td>
<td>Grass pollen–induced RCA with or w/out asthma</td>
<td>Improved TCS by 20% ($P_{=.005}$), DSS by 18% ($P_{=.02}$), and RQLQ(S) scores by 17% ($P_{=.02}$). DMS were improved by 26% ($P_{=.08}$). No treatment-related serious AEs or reports of anaphylactic shock/respiratory compromise.</td>
</tr>
<tr>
<td>Maloney 2014&lt;sup&gt;23&lt;/sup&gt;</td>
<td>5-65</td>
<td>1501 total (A + P)</td>
<td>137/104</td>
<td>TGP</td>
<td>4-8 mos before and during grass pollen season continued for 3 seasons; 2-yr blinded follow-up</td>
<td>Grass pollen–induced RCA with or w/out asthma</td>
<td>Improvements ($P_{&lt;.001}$) vs placebo of 23% in entire-season TCS, 29% in peak-season TCS, 20% in entire-season DSS, 35% in entire-season DMS; 12% in peak-season RC QOL questionnaire ($P_{=.027}$). No serious treatment-related AEs or anaphylactic shock.</td>
</tr>
<tr>
<td>Durham 2012&lt;sup&gt;24&lt;/sup&gt;</td>
<td>18-65</td>
<td>137/104</td>
<td>NS</td>
<td>TGP</td>
<td>4-8 mos before and during grass pollen season continued for 3 seasons; 2-yr blinded follow-up</td>
<td>Grass pollen–induced RCA</td>
<td>SLIT vs placebo: Mean RC DSS was reduced by 25%-36% ($P_{&lt;.004}$) over the 5 grass pollen seasons covered. RCV DMS was reduced by 20%–45% ($P_{&lt;.02}$ for seasons 1–4; $P_{=.114}$ for season 5). Weighted RC combined score was reduced by 27%-41% ($P_{&lt;.003}$). Percentage of days with severe symptoms during the peak grass pollen exposure was lower in all seasons in the active group than in the placebo group (relative differences of 49% to 63% ($P_{&lt;.0001}$). No treatment-related serious AEs or events of severe systemic allergic reactions.</td>
</tr>
<tr>
<td>Cox 2012&lt;sup&gt;25&lt;/sup&gt;</td>
<td>18-65</td>
<td>233/240</td>
<td>26/17</td>
<td>TGP</td>
<td>6-mo preseasonal and coseasonal treatment and 2-wk follow-up</td>
<td>Grass pollen–induced RCA</td>
<td>The mean daily combined score over the pollen period was significantly lower w/SLIT vs placebo (LSM difference, -0.13; 95% CI, -0.19 to -0.06; $P_{=0.003}$; relative reduction, 28.2%; 95% CI, -13.0% to -43.4%). There were no reports of anaphylaxis, and no actively treated participant received epinephrine.</td>
</tr>
<tr>
<td>Didier 2007&lt;sup&gt;26&lt;/sup&gt;</td>
<td>18-45</td>
<td>472/156</td>
<td>59/10</td>
<td>TGP</td>
<td>4 mos prior to pollen season and continued throughout season</td>
<td>Grass pollen–induced RCA</td>
<td>Significantly reduced mean RC TSS (3.58 ± 3.0, $P_{=.0001}$; and 3.74 ± 3.1, $P_{=.0006}$ for 300-IR and 500-IR doses) vs placebo (4.93 ± 3.2). No serious systemic events or anaphylactic shock were observed.</td>
</tr>
</tbody>
</table>
Safety

Based on more than 30 years of clinical use and more than 80 randomized, controlled trials, the safety profile of SLIT has been shown to be superior to SCIT.\textsuperscript{39} No fatalities and few cases of anaphylaxis have been reported, with well over 1 million SLIT doses administered in clinical trials (as of 2006) and an estimated 1 billion doses administered worldwide between 2000 and 2012.\textsuperscript{40}

Oral side effects (oral or ear pruritus, throat irritation, tongue pruritus, and mouth edema) are common with SLIT, affecting approximately 50% of patients, but typically last 10 days or less, and are infrequently (less than 5%) associated with discontinuation.\textsuperscript{39} The occurrence and severity of adverse events declines in subsequent years of treatment. A low frequency of gastrointestinal side effects (eg, diarrhea, nausea, and abdominal pain) also may be observed.

Despite the extremely low incidence of systemic serious adverse reactions to SLIT, it is important to be familiar with potential factors that may increase the risk for its occurrence (\textit{TABLE 2}).\textsuperscript{40} Most important among these is severe, unstable, or uncontrolled asthma, which represents an absolute contraindication to SLIT (as well as to SCIT).\textsuperscript{39} SLIT should also be avoided in patients with medical conditions that may reduce the ability to survive a serious allergic reaction or increase the risk for adverse reactions after epinephrine administration (eg, markedly compromised lung function, unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension). SLIT may not be suitable for patients receiving medications that can potentiate or inhibit the effects of epinephrine (eg, beta-adrenergic blockers, alpha-adrenergic blockers, and tricyclic antidepressants).\textsuperscript{13-15}

\begin{table}[h]
\centering
\caption{Randomized, double-blind, placebo-controlled trials of SLIT tablets for grass and ragweed pollen (Continued)}
\begin{tabular}{|l|l|l|l|l|l|l|
\hline
\textbf{Study} & \textbf{Age range (y)} & \textbf{A/P} & \textbf{Dropouts (A/P)} & \textbf{Product tested} & \textbf{Duration} & \textbf{Results} \\
\hline
Didier & 18-50 & 414/219 & 117/56 & 5-GPAE & Either 2 or 4 mos before and then during grass pollen season for 3 consecutive seasons & Grass pollen–induced RCA & Mean AAdSS was reduced by 37.7% and 34.8% at season 3 in the 2- and 4-month preseasonal and coseasonal active treatment groups, respectively, vs placebo ($P < .0001$ for both). 1 severe local reaction and 1 angioedema during first year, resulting in study discontinuation. \\
Wahn & 5-17 & 139/139 & 8/4 & 5-GPAE & 4 mos before estimated pollen season and continued throughout season & Grass pollen–induced RCA & The 300-IR group showed a mean improvement for the RTSS of 28.0% over that seen with placebo ($P = .001$) and a median improvement of 39.3%. AEs were generally mild or moderate in intensity and expected. No serious side effects were reported. \\
Creticos & 18-50 & 586/198 & 140/38 & SRPAE & 52 wks of daily SLIT & Short ragweed–induced RCA & During peak season, low, medium, and high doses of SLIT reduced TCS by 9% (-0.76; $P = .22$), 19% (-1.58; $P = .01$), and 24% (-2.04; $P = .002$) compared with placebo. No systemic allergic reactions occurred. \\
Nolte & 18-50 & 377/188 & 100/42 & SRPAE & 12 wks before and during entire ragweed season and thereafter up to 52 wks & Short ragweed–induced RCA & During peak season, the low and high ragweed AIT doses showed 21% (-1.76 score; $P = .004$) and 27% (-2.24 score; $P < .001$) improvement in TCS vs placebo. No systemic allergic reactions were reported. One patient in the treatment group received epinephrine at an emergency facility for sensation of localized pharyngeal edema. \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Abbreviations: AE, adverse event; AAdSS, average adjusted symptom score; AIT, allergy immunotherapy tablet; A/P, active/placebo; CI, confidence interval; DMS, daily medication score; DSS, daily symptom score; IR, index of reactivity; LSM, least-squares mean; NS, not stated; QOL, quality of life; RC, rhinoconjunctivitis; RCA, rhinoconjunctivitis/asthma; RQLQ(S), Standardized Rhinoconjunctivitis Quality of Life Questionnaire; RTSS, Rhinoconjunctivitis Total Symptom Score (RTSS); SLIT, sublingual immunotherapy; SRPAE, short ragweed pollen allergen extract; TCS, total combined score; TGPAE, Timothy grass pollen allergen extract; 5-GPAE, 5-grass pollen allergen extract; TSS, total symptom score.}
Key points for primary care providers

While best practices to guide the use of SLIT tablets are still evolving, some key points regarding patient management are summarized below.

It is essential that patient sensitivity to the specific seasonal allergen is confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies to the specific pollen in order to guide appropriate therapy. The in vitro, enzyme-linked immunosorbent assay (ELISA) test now recommended is an improvement over the radioallergosorbent test (RAST). SLIT is typically indicated for treatment of moderate to severe intermittent or persistent AR symptoms, particularly in patients who do not respond well to pharmacotherapy and environmental modification. These same considerations would likely be associated with perennial allergens.

Efficacy and safety of SLIT in children are similar to adults, and the 1- and 5-grass pollen products are indicated for children as young as 5 and 10 years old, respectively.

Although patients with asthma were included in clinical trials of SLIT products, their asthma was well-controlled. Therefore, caution should be used when initiating SLIT in patients with moderate-to-severe persistent and high-risk asthma, and SLIT should not be initiated or dosed at any time in patients with uncontrolled asthma. Other potential risk factors for SLIT-related anaphylaxis to be considered in patient selection for SLIT are listed in Table 2.

New-onset eosinophilic esophagitis has been reported to occur after initiation of SLIT and to be resolved after discontinuation of SLIT. Therefore, a history of eosinophilic esophagitis is a contraindication to initiation of SLIT. Patients on SLIT should be counseled to report worsening dysphagia and/or heartburn.

The 1-grass pollen and ragweed pollen SLIT products are approved for treatment initiation at least 12 weeks before, and the 5-grass pollen product 16 weeks before, the expected onset of each grass or ragweed pollen season. All 3 products are continued throughout the season and then stopped. The patient should be instructed to remove the tablet from the blister pack with dry hands and to place it immediately under the tongue, allowing it to dissolve, and to avoid food or beverage for 5 minutes. Hands should be washed after handling the tablet.

The 5-grass mixed pollen SLIT product is dosed once daily, with no increase in dose for adults 18 to 65 years of age. For children 10 to 17 years of age, the dose is increased over the first 3 days to achieve the maintenance dose.

For initiation of SLIT-tablet therapy, the first dose is administered by the provider, followed by a 30-minute observation period to monitor for signs or symptoms of a severe systemic or local allergic reaction. Epinephrine and other measures to treat anaphylaxis should be immediately available to the provider, and an epinephrine auto-injector should be prescribed for home use with instructions for when and how to use it. If the patient tolerates the first dose of SLIT, subsequent doses can be given at home. The patient should be instructed to remove the tablet from the blister pack with dry hands and to place it immediately under the tongue, allowing it to dissolve, and to avoid food or beverage for 5 minutes. Hands should be washed after handling the tablet.

For mild-to-moderate oral adverse events and mild abdominal pain and nausea, antihistamine H1 and H2 blockers may be helpful. Patients experiencing severe or recurrent symptoms should be instructed to contact the prescriber and consider stopping SLIT. To minimize the risk of serious harm, patients must be taught how to monitor for signs of rapidly progressing reactions, such as worsening laryngeal edema, urticaria, or shortness of breath, that may require epinephrine use. Once suspected, anaphylaxis must be treated with an intramuscular injection of epinephrine, as death can occur.

### TABLE 2: Potential risk factors for SLIT-associated anaphylaxis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overdose</td>
<td>Interrupts in dose regimen</td>
</tr>
<tr>
<td>Previous systemic reaction, including anaphylaxis, to SCIT or SLIT</td>
<td></td>
</tr>
<tr>
<td>Previous severe local reaction</td>
<td></td>
</tr>
<tr>
<td>Asthma (particularly if severe or uncontrolled)</td>
<td></td>
</tr>
<tr>
<td>Acute infection (eg, upper respiratory infection)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Oral infections or lesions (eg, ulcer, gingivitis, periodontitis, etc) due to SLIT</td>
<td></td>
</tr>
<tr>
<td>Gender (premenstrual status)</td>
<td></td>
</tr>
<tr>
<td>Young age</td>
<td></td>
</tr>
<tr>
<td>Emotional stress</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
</tr>
<tr>
<td>High pollen counts</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** SCIT, subcutaneous immunotherapy; SLIT: sublingual immunotherapy.

within minutes. If SLIT is being administered to a child, the parent or other responsible adult must administer each dose and monitor the child for any serious allergic reaction. Transitioning patients from SCIT to SLIT should be guided by the expertise of an allergist or immunology specialist. Concomitant administration of SCIT and SLIT has not been well-studied. Currently, there is no procedural terminology (CPT) code for billing purposes for SLIT administration.

Lastly, the cost of AIT varies widely. Data from 8 preferred provider organizations showed 60% to 80% coverage for SCIT, with weekly copays of $0 to $50 and deductibles from $0 to $700. Medicare had a flat rate of 80% coverage, costing the insurer $807.20 for a year of SCIT. The study also showed that the cost of SLIT ranged from $500 to $2100, depending on the allergy practice and the number of antigens treated. Another study showed that the total direct medical costs for SCIT were $32 per visit (range $13 to $61), with half accounted for by the cost of the extract. Pre- and post-injection administrative tasks were the second largest driver of direct costs.

REFERENCES

The Primary Care Metabolic Group (PCMG) is a national educational initiative providing comprehensive metabolic disease education. PCMG’s mission is to provide a representative forum for primary care clinicians involved in metabolic disease management and raise standards of patient care through the dissemination of best practices, education programs, and communication among members.

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