A SPECIAL SUPPLEMENT ON
Hot Topics in Primary Care

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Introduction

Primary care clinicians provide the vast majority of outpatient care in the United States. In fact, 77.8% of all nurse practitioners deliver primary care.1 Additionally, 19.9% and 5.2% of all certified physician assistants practice in family medicine and internal medicine, respectively.2,3 Because of this reality, it is incumbent upon us to manage common conditions uncommonly well.

Our core precepts, encompassed by the 4 C’s: first Contact, Continuity, Comprehensiveness, and Coordination of care, are explicated throughout the supplement. Because clinical content in primary care is diverse, in this third annual Hot Topics Supplement, we cover 6 different areas that are particularly relevant to your daily practice.

This supplement addresses developments and new considerations in therapy, as well as provides a review of diagnostic criteria. We trust that you will find this special issue contains useful and practical information that will assist in the daily management of your patients.

Another supplement to the journal will be developed next year, and we welcome your input and suggestions of areas that we should cover. Your input this year was invaluable, and we thank you.

Stephen A. Brunton, MD, FAAFP
Executive Vice President
Primary Care Education Consortium

REFERENCES
Approach to the Identification and Differentiation of Migraine

Merle L. Diamond, MD; Susan Hutchinson, MD

CASE SCENARIO

Elise is a 43-year-old woman who presents for a 6-month follow-up for type 2 diabetes mellitus. Although her diabetes is well-controlled, Elise's primary care physician (PCP) notices numerous gaps in blood glucose levels when reviewing Elise's diabetes log. The PCP also notes that Elise is tired and in some distress. Upon questioning, Elise indicates that she was awake most of the night because of throbbing headache pain.

Nearly one in four US households includes a person with migraine.\(^1\) Approximately 18% of women and 9% of men in the US experience migraine during their lifetime.\(^2\)

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DISCLOSURES

Dr. Diamond discloses that she is on advisory boards and a consultant for Alder BioPharmaceuticals Inc.; Amgen Inc.; Promius Pharma, LLC; and Teva Pharmaceutical Industries Ltd. She is on the speakers' bureaus for Amgen Inc.; Avanir Pharmaceuticals, Inc.; Depomed, Inc.; Perlix Therapeutics; Supernus Pharmaceuticals, Inc.; and Teva Pharmaceutical Industries Ltd. She is on the advisory boards for Avanir Pharmaceuticals, Inc.; Depomed, Inc.; Eli Lilly and Company; Supernus Pharmaceuticals, Inc.; and Upsher-Smith Laboratories. Dr. Diamond is on the Board of Directors for the National Headache Foundation and the Diamond Headache Clinic Research and Educational Foundation.

Dr. Hutchinson discloses that she has served as a consultant and is on the advisory boards for Alder Biopharmaceuticals Inc.; Allergan plc; Amgen Inc.; Avanir Pharmaceuticals, Inc.; electroCore, LLC; Eli Lilly and Company; Supernus Pharmaceuticals, Inc.; and Teva Pharmaceutical Industries Ltd. She is on the speakers' bureaus for Allergan plc; Avanir Pharmaceuticals, Inc.; Perlix Therapeutics; and Supernus Pharmaceuticals, Inc. She has participated in research studies for GlaxoSmithKline plc.

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IMPROVING THE DIAGNOSIS OF MIGRAINE IN PRIMARY CARE: WHY IT’S IMPORTANT

Why is improving the diagnosis of migraine important? Consider these facts.

• Migraine is the second leading cause of disability worldwide.\(^3\)
• Migraine morbidity is not limited to attacks; between attacks, one-quarter of people with migraine reported symptoms such as anxiety, lack of freedom from headache symptoms, and avoidance of any activities.\(^4\)
• Some of the more prevalent comorbidities with migraine include ischemic stroke, myocardial infarction, depression, anxiety, bipolar disorder, panic disorder, chronic pain, hypertension, and hyperlipidemia.\(^4,9\)
• Approximately 1 in 8 people with migraine report they have done less well in their education because of their headaches.\(^4\)
• Children of parents with migraine report a significant impact on their lives, including reverse caregiving, moderate-to-severe anxiety, and moderate-to-severe depression.\(^10\)
• Patients with chronic migraine commonly report the belief that nothing can control migraine onset and course.\(^7\)

These findings make it clear that people with migraine experience significant morbidity, which also affects families and employers, yet a high proportion don’t seek medical care.\(^11\) An early, accurate diagnosis of migraine may lead to better medical management and improved patient outcomes.

CASE SCENARIO (CONT)

Elise further reports that she has experienced similar headaches since her twenties. The headaches became more frequent and painful when she became a supervisor at a local factory about 5 years ago. She doesn’t experience any visual or auditory sensations before or during the attack, but she generally experiences nausea. In addition, pain is worsened with routine activity such that she finds it difficult to function during an attack. She has tried various OTC analgesics.
DIAGNOSIS
An important first step in headache diagnosis is to determine if the headache is a primary or secondary headache. For primary headaches, eg, migraine, cluster, and tension-type, the headache is the disease. In contrast, secondary headaches are caused by something else (eg, infection, trauma, mass, vascular abnormality). 

Differentiating secondary from primary headaches
Differentiating primary from secondary headaches begins with the search for “red flags” that might suggest a secondary headache. Several tools are available to clinicians for identifying red flags; one helpful mnemonic is SNOOP4 (FIGURE). The presence of a red flag does not confirm a secondary headache.

The assessment for red flags begins with a detailed history and physical and neurological examination. Although the majority of patients with headache will have normal examinations, those with an abnormality may warrant imaging or other studies to rule out secondary headache. In the primary care setting, the need for imaging is limited. Findings from the pertinent medical history suggesting a need for imaging or other studies include change in headache pattern, frequency, severity; abnormal neurological signs or symptoms; headaches associated with trauma or new onset seizures; or headaches in patients with a history of cancer, human immunodeficiency virus, or active infection. Magnetic resonance imaging is the preferred method of imaging in nonacute headache. In the emergency department setting, imaging should be considered if red flags are present. When they are encountered, computed tomography is useful to assess for subarachnoid hemorrhage, head trauma, and bony abnormalities. If a secondary headache can be excluded by history, physical and neurological examination, or appropriate testing, the next step is to identify the primary headache disorder.

Identifying the type of primary headache
As in identifying patients with secondary headache, the history is vitally important in the diagnosis of primary headache, including migraine. Consequently, patients should be provided adequate time to fully describe the headaches and how they have been self-managing, including the use of complementary and alternative therapies. Issues to explore are listed in TABLE 1.

The patient’s medical history, including associated disorders, and social history should be reviewed or, if unknown, investigated in detail. When it comes time to develop the treatment plan, addressing associated disorders that may be modifiable should be considered as this may be helpful in improving patient outcomes.

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<th>Systemic symptoms/signs/disease</th>
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<td>• Postural aggravation</td>
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Patients may have more than one type of primary headache. Therefore, to simplify the diagnostic evaluation, the most severe headache should be the initial focus. This can be facilitated by asking the patient to describe the headache that causes them the greatest disability. To assess disability, validated questionnaires such as the Headache Impact Test (HIT-6) or the Migraine Disability Assessment Questionnaire (MIDAS) may be used.

Migraine is a neurologic disease that includes headache characterized by a unilateral, throbbing pain with concurrent nausea and/or vomiting. Migraine symptoms can vary in patients with migraine. The aforementioned are some of the characteristics that may be experienced by patients with migraine, but may not always be present.

For example, migraine is unilateral in approximately 54% to 67% of patients. Similarly, only about 13% to 41% of patients with migraine experience aura. When nausea is present ≥50% of the time with headache, it has been shown to be associated with a two-fold increased risk of progression from episodic to chronic migraine over 2 years of follow up compared to those with no or low frequency of nausea.

Symptoms occurring hours or days before and/or during the migraine attack appear to be common. These commonly include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue, neck stiffness, and/or pain. Patients may find it difficult to provide all of the needed information during the history.

If so, the use of a headache diary may be considered. Identifying patients with migraine can be challenging. One reason is that patients may experience one or more types of headache. In addition, the frequency, signs and symptoms, and associated disability of migraine may vary over time, even within the same day.
As with some other types of headache, migraine is often classified as either episodic or chronic, the only difference is in their frequency. Migraine is considered chronic if headache occurs on ≥15 days/month for ≥3 months, which, on ≥8 days/month, has the features of migraine headache. Migraine headache on ≤14 days per month is referred to as episodic migraine in migraine research; the International Classification of Headache Disorders, 3rd edition (ICHD-3) does not have a category specifically for episodic migraine. Although disability due to chronic migraine is greater, patients with episodic migraine may also experience substantial disability.

The American Migraine Prevalence and Prevention (AMPP) study was conducted from 2004 to 2009 to describe migraine prevalence, sociodemographic profiles, burden, comorbidity patterns, prognosis, and health-related outcomes. Results from 5681 eligible study respondents with episodic migraine in 2006 revealed that patients who received inadequate efficacy from their acute treatment were at increased risk of new-onset chronic migraine. Over a one-year period, progression of migraine from episodic to chronic was assessed based on 4 defined categories of migraine treatment efficacy. Increasing progression with decreased treatment efficacy was a key finding: maximum efficacy (1.9%), moderate efficacy (2.7%), poor efficacy (4.4%), and very poor efficacy (6.8%). Triptan use was highest in the maximum efficacy group, while opioid or barbiturate use was highest in the moderate and poor efficacy groups.

Despite thorough assessment, it may not be appropriate to make a definitive diagnosis of migraine. In fact, current ICHD-3 classification schema includes categories of “probable migraine” and "headache unspecified." The updated ICHD-3 was developed by the International Headache Society to guide classification of headache disorders using evidence-based diagnostic criteria. Even so, in the absence of a definitive diagnosis of other primary or secondary headache, if the patient experiences substantial disability, migraine may be the likely diagnosis. Finally, it should be remembered that patients often have more than one type of headache, often with overlapping and/or fluctuating symptoms. Consequently, it is important to periodically reassess the diagnosis to ensure that the patient is receiving optimal care.

**COMMON QUESTIONS**

*Is there a quick way to diagnose migraine?*

Although the diagnosis of migraine is generally based on the history and physical examination, the use of a validated screener such as ID Migraine may be useful once a secondary headache has been ruled out. Development of the ID Migraine screener was based on the existing 1988 ICHD criteria using 9 screening questions. Among these, a three-item subset assessing disability, nausea, and photophobia...
(TABLE 3) provided optimal performance in the primary care setting. Testing showed that the optimal total score in the primary care setting was any combination using 2 of the 3 questions with a sensitivity of 81% (95% confidence interval (CI) 77%-85%) and specificity of 75% (95% CI 64%-84%). Using all three questions provided a positive predictive value of 93% (95% CI 89.9%-95.8%) and good test-retest reliability (kappa 0.68, 95% CI 0.54-0.82). The sensitivity and specificity were similar regardless of age, presence of comorbid headaches, or previous diagnostic status; the sensitivity was slightly lower and the specificity higher in men than women.

What kind of information should be captured using a headache diary?

Patients’ headache diaries can be used to provide information assessed during history taking (TABLE 1). It can be very helpful in identifying and modifying factors that influence a patient’s headaches, including triggers. This information can be useful to differentiate modifiable (e.g., light, stress, caffeine, alcohol) from nonmodifiable (menstruation for females, environmental) factors, targeting treatment at those that are modifiable. Diaries are available from several sources:


**REFERENCES**

Long-term Treatment of Gout: New Opportunities for Improved Outcomes

Paul P. Doghramji, MD, FAAA-PH

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES
- Make a presumptive diagnosis of gout based on history and physical examination
- Individualize and modify urate-lowering therapy based on best evidence to achieve treatment goals

TARGET AUDIENCE
Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of the long-term treatment of gout.

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Paul P. Doghramji, MD discloses that he is on the advisory board for Ironwood Pharmaceuticals, Inc. and owns stock in Pfizer, Inc.

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METHOD OF PARTICIPATION
PHYSICIANS
To receive CME credit, please read the journal article and on completion, go to www.pceconsortium.org/gout to complete the online post-test and receive your certificate of completion.

PHYSICIAN ASSISTANTS
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WHAT DO THE 3 FOLLOWING REAL-LIFE CASES HAVE IN COMMON?
1. An adult male presenting with pain in the foot and instep
2. A postmenopausal female presenting with wrist pain and stiffness
3. A young, thin male presenting with severe pain in the mid-foot, similar to what his father and brother experience.

The underlying cause of pain in all 3 of these patients is undiagnosed gout, demonstrating different presentations of gout.

This article will discuss some of the key questions and clinical challenges encountered in the long-term primary care management of patients with gout.

Paul P. Doghramji, MD, FAAA-PH, Family Physician, Collegeville Family Practice, Medical Director of Health Services, Ursinus College, Collegeville, Pennsylvania

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Dr. Doghramji discloses that he is on the advisory board for Ironwood Pharmaceuticals, Inc.; and owns stock in Pfizer Inc.

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ARE THERE CONSEQUENCES OF GOUT BEYOND IMPAIRED FUNCTIONING AND QUALITY OF LIFE?
Gout is an independent predictor of premature death and is associated with a high frequency of comorbidities, many with a prevalence 2 to 3 times higher than among people without gout: hypertension, chronic kidney disease (CKD), obesity, type 2 diabetes, nephrolithiasis, cardiac disease (including coronary artery disease, heart failure, and atrial fibrillation), dyslipidemia, stroke, peripheral arterial disease, and sleep apnea.1-3

DO ALL PATIENTS WITH HYPERURICEMIA DEVELOP GOUT?
Based on an estimated prevalence of gout of 3.9% (8.3 million) and hyperuricemia (ie, serum uric acid [sUA] level >7.0 mg/dL in men and >5.7 mg/dL in women) of 21.4% (43.3 million) among US adults, approximately 1 in 5 people with hyperuricemia develop symptoms of gout.4 Although the prevalence of hyperuricemia is similar among men (21.2%) and women (21.6%), the prevalence of gout is approximately 3 times higher in men than in women (5.9% and 2% of adults in the United States, respectively); the disparity between sexes lessens after menopause.5 The overall prevalence of gout increases with age, from 3.3% in adults over the age of 40 years to 9.3% in adults over the age of 70 years.4 Family history may also play a small role.

CASE STUDY, STEVE:
A 37-year-old male with obesity (body mass index, 33 kg/m²) presents with a painful, swollen big toe. He has a family history of gout (father, brother). sUA is 7.3 mg/dL.

WHAT ARE THE COMMON FINDINGS ON HISTORY AND PHYSICAL EXAMINATION THAT SUGGEST GOUT?
An acute gout attack (flare) is typically monoarthritic early in the disease and peaks within hours, manifesting as a severely inflamed joint that is red, hot, swollen, and tender to the touch or movement.6 The attack is self-limiting, with symptoms resolving within about 2 weeks, although ongoing joint damage during intercritical asymptomatic periods usually occurs due to continuing monosodium urate (MSU) crystal deposition and inflammation.7 An acute attack most commonly manifests in the lower extremities, particularly the first metatarsophalangeal joint (podagra) in men, whereas the elbow, wrist, and hands are more likely to be affected in women.6,8 The reduced solubility of urate at lower temperatures may account for the occurrence of gout at peripheral joints, which are cooler than central-axis joints.8 Involvement of more than 1 joint is more common as disease progresses.6

WHAT, IF ANY, FURTHER ASSESSMENT IS NEEDED BEYOND THE HISTORY AND PHYSICAL EXAMINATION TO CONFIRM THE DIAGNOSIS OF GOUT?
The most important component of the differential diagnosis of acute gout is septic arthritis, although the incidence of septic arthritis is much lower. In addition, the onset of septic arthritis is more insidious, and patients with septic arthritis tend to be quite sick with fever, rash, or other signs of systemic illness, and typically require hospitalization.8,10

Synovial fluid aspiration and identification of MSU crystals by polarized light microscopy is the gold standard of gout diagnosis.6 However, an adequate clinical analysis is sufficient for diagnosis in most cases, so this test is often not required.11 Combined with intra-articular corticosteroid injection, joint aspiration provides immediate and lasting pain relief for many patients.6,8 Radiography is not useful in early gout because small erosions and tophi are difficult to detect, but such lesions are detectable in chronic gout.6 Although not commonly done, ultrasonography is useful in early gout to distinguish between active and inactive tophi.6

The absence of hyperuricemia is inadequate alone to rule out a gout diagnosis because the sUA level may drop to normal during a gout attack. Therefore, even though it is reasonable to measure sUA during an attack, the sUA level should be measured again several weeks after the flare has resolved.10 It should be kept in mind that each laboratory calculates its own sUA threshold for hyperuricemia, so a “normal” sUA level may, nevertheless, reflect levels in joint tissues that are above ~6.8 mg/dL necessary for MSU crystal deposition.7 Most labs these days will also list, “sUA desirable level for gout treatment: <6.0 mg/dL.”

Hyperuricemia and gout should be considered red flags for metabolic syndrome and cardiovascular disease. Therefore, additional evaluation includes a comprehensive metabolic panel (eg, blood glucose and hemoglobin A1c levels and kidney and liver function) and a lipid panel, as well as clinical screening for associated comorbidities and cardiovascular risk factors (eg, obesity, hypertension, smoking).12,13

CASE STUDY, STEVE (CONTINUED)
A diagnosis of gout is confirmed. A plan is developed to begin a nonsteroidal anti-inflammatory drug for acute treatment for the flare. Once the flare has resolved, urate-lowering therapy will be initiated.
WHAT ARE THE OBJECTIVES OF LONG-TERM GOUT MANAGEMENT?

Monosodium urate crystal formation is reversible, and crystals will dissolve when the sUA level drops below the limit of solubility (~6.8 mg/dL). This will result in the disappearance of gout flares and a reduction in the size and number of tophi.\(^1,2,4\) The lower the sUA level, the faster the crystal deposits (and tophi) resolve. Therefore, the goal of long-term gout management is to lower the sUA level below the limit of solubility.\(^4\) In addition, the management of patients with gout should include prevention and treatment of associated cardiovascular and other diseases.\(^3\)

WHAT IS THE TARGET SUA GOAL?

According to both the American College of Rheumatology (ACR) guidelines and the European League Against Rheumatism (EULAR) recommendations, the target sUA goal for urate-lowering therapy (ULT) is <6 mg/dL for all gout patients. A lower sUA target (<5 mg/dL) to facilitate faster dissolution of crystals is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks) until total crystal dissolution and resolution of gout are achieved.\(^1,2,4\)

Appropriately treated gout, with maintenance of sUA below target levels, markedly reduces the frequency of gout flares and the size and number of tophi and improves quality of life (QoL).\(^12\) Inadequate treatment that fails to maintain sUA below target levels is associated with recurrent flares, further joint damage, and subsequent loss of mobility, functional impairment, and decreased QoL.\(^11\)

HOW OFTEN SHOULD SUA BE MONITORED?

The American College of Radiology guidelines recommend monitoring sUA every 2 to 5 weeks during ULT titration (see “How is each of the approved ULTs initiated and titrated?,” on page S23), then every 6 months once the sUA target level is achieved.\(^15\)

DOES LIFESTYLE MANAGEMENT HAVE A ROLE?

Evidence from randomized, blinded studies is lacking regarding alteration of lifestyle factors translating into improved outcomes in patients with gout. However, diet, exercise, and weight loss have been associated with a modest reduction in the sUA level in some clinical trials; therefore, every patient should be encouraged to make such changes as best as possible.\(^12,15\) Lifestyle management (eg, reducing excess body weight, regular exercise, smoking cessation, and avoiding excessive alcohol and sugar-sweetened drinks) has a greater role in reducing the risk and optimizing management of life-threatening comorbidities in patients with gout.\(^12,13,15\)

WHAT MEDICATIONS ARE APPROVED IN THE UNITED STATES AS ULT? WHAT IS THE MECHANISM OF ACTION OF EACH MEDICATION?

Available US Food and Drug Administration (FDA)-approved options for lowering sUA include xanthine oxidase inhibitors (allopurinol and febuxostat) that prevent production of uric acid; a uricosuric agent (probenecid) that increases uric acid output in urine; and a uric acid-specific enzyme (pegloticase) that converts uric acid to allantoin. Another recently approved uricosuric agent, lesinurad, inhibits the function of transporter proteins (urate transporter 1 and organic anion transporter 4) involved in uric acid reabsorption in the kidney.\(^6,16\)

Fenofibrate, losartan, and atorvastatin are not FDA-approved for gout but act as uricosurics and can therefore be used to treat gout comorbidities or in association with xanthine oxidase inhibitors.\(^6\) There has been limited study of rasburicase, an injectable approved for tumor lysis, in the treatment of tophaceous gout.\(^16\)

CASE STUDY, HARRIET:

In a patient diagnosed with gout (and who has normal renal function), allopurinol, 300 mg daily, is initiated after resolution of an acute flare. sUA is reduced from 8.6 mg/dL to 7.2 mg/dL after 9 months of treatment. Clinical decision points:

- Should the dosage of allopurinol be increased or should a non-xanthine oxidase inhibitor be initiated?
- If the patient’s estimated glomerular filtration rate is 35 mL/min/1.73 kg/m\(^2\), would this impact the decision between uptitrating and adding a second agent?

WHAT ARE THE RECOMMENDATIONS AND EVIDENCE FOR EACH ULT?

Guidelines recommend a xanthine oxidase inhibitor as first-line therapy.\(^15\) Allopurinol is most commonly used due to its low cost, extensive clinical experience, and relatively good safety and efficacy profile.\(^8,13\)

For patients who do not achieve the target sUA level with optimized allopurinol therapy, the next-step choice is primarily a consideration of patient-specific factors, physician and patient choice, and cost. In the author’s experience, a good option is using medications with different mechanisms of action because this provides further lowering of sUA while enabling the use of lower dosages of individual medications, thereby reducing the incidence and severity of dosage-related adverse events.

The xanthine oxidase inhibitor febuxostat, 80 mg/d or 120 mg/d (the latter an investigational dose but recommended by ACR and EULAR when needed) has demonstrated superior urate-lowering efficacy compared with allo-
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<th>Study/author</th>
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<td>Percentage of patients with sUA &lt;6 mg/dL at last 3 monthly measurements</td>
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<td>ALP 300 mg/d (n=253)</td>
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<td>FBX 80 mg/d (n=256)</td>
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<td>APEX/Schumacher(^{19})</td>
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<td>LSN 400 mg/d + ALP: 59.2% ((P&lt;.0001))^a</td>
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<td>CRYSTAL/Dalbeth(^{22})</td>
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<td>Percentage of patients with sUA &lt;5 mg/dL by month 6</td>
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<td>PBO/FBX 80 mg/d (n=109)</td>
<td>PBO/FBX 80 mg/d: 46.8%</td>
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<td>LSN 200 mg/d + FBX 80 mg/d (n=106)</td>
<td>LSN 200 mg/d + FBX 80 mg/d: 56.6% ((P=.13))^a</td>
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<td>LSN 400 mg/d + FBX 80 mg/d (n=109)</td>
<td>LSN 400 mg/d + FBX 80 mg/d: 76.1% ((P&lt;.0001))^a</td>
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<td>Open label study/Reinders(^{24})</td>
<td>Stage 1: 2 months</td>
<td>Percentage of patients attaining sUA &lt;0.3 mmol/L(^{c})</td>
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<td>ALP 200-300 mg/d (based on renal function) (n=32)</td>
<td>Stage 1</td>
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<td></td>
<td>Probenecid 1000 mg/d, added to ALP in patients failing to attain sUA &lt;0.3 mmol/L (n=14)</td>
<td>Stage 2</td>
</tr>
<tr>
<td></td>
<td>ALP monotherapy: 25%</td>
<td>ALP plus probenecid: 86%</td>
</tr>
<tr>
<td>CO405/Sundy(^{25})</td>
<td>6 months</td>
<td>Percentage of patients with sUA &lt;6 mg/dL ≥80% of the time at Month 3 and Month 6</td>
</tr>
<tr>
<td></td>
<td>Group 1: Pegloticase 8 mg biweekly (n=43)</td>
<td>Group 1: 47% (95% CI, 31%-62%)</td>
</tr>
<tr>
<td></td>
<td>Group 2: Pegloticase 8 mg monthly (n=41)</td>
<td>Group 2: 20% (95% CI, 9%-35%)</td>
</tr>
<tr>
<td></td>
<td>Group 3: Placebo (n=20)</td>
<td>Group 3: 0</td>
</tr>
<tr>
<td>CO406/Sundy(^{25})</td>
<td>6 months</td>
<td>Percentage of patients achieving sUA &lt;6 mg/dL ≥80% of the time at Month 3 and Month 6</td>
</tr>
<tr>
<td></td>
<td>Group 1: Pegloticase 8 mg biweekly (n=42)</td>
<td>Group 1: 38% (95% CI, 24%-54%)</td>
</tr>
<tr>
<td></td>
<td>Group 2: Pegloticase 8 mg monthly (n=43)</td>
<td>Group 2: 49% (95% CI, 33%-65%)</td>
</tr>
<tr>
<td></td>
<td>Group 3: Placebo (n=23)</td>
<td>Group 3: 0</td>
</tr>
</tbody>
</table>

\(^{a}\)Compared with allopurinol-based arm. 
\(^{b}\)10 subjects received 100 mg/d and 258 subjects received 300 mg/d, based on renal function. 

\(^{c}\)sUA, 0.3 mmol/L = ~5.0 mg/dL. 

**Abbreviations:** ALP, allopurinol; CI, confidence interval; FBX, febuxostat; LSN, lesinurad; PBO, placebo; sUA, serum uric acid.
purinol at a fixed dosage of 300 mg/d (TABLE).\textsuperscript{12,17-19} Although ACR guidelines do not give preference to allopurinol or febuxostat, EULAR and other international guidelines recommend that febuxostat be used in patients who are intolerant of, or do not respond to, an adequate dosage of allopurinol.\textsuperscript{12,13,15} Febuxostat has been associated with cutaneous reactions, but data do not support any cross-reactivity with allopurinol.\textsuperscript{12} Liver function abnormalities and a slightly higher incidence of cardiovascular thromboembolic events may occur.\textsuperscript{20}

Guidelines also recommend adding a uricosuric agent (lesinurad or probenecid) or switching to a uricosuric agent (probenecid) if the sUA target level cannot be reached by an appropriate dosage of a xanthine oxidase inhibitor or when a xanthine oxidase inhibitor is not tolerated.\textsuperscript{12,13,15} The efficacy of probenecid in combination with allopurinol in such patients has been demonstrated in a few small trials.\textsuperscript{21} However, probenecid is not recommended in patients with a creatinine clearance <50 mL/minute or uric acid urolithiasis.\textsuperscript{15}

Lesinurad is approved only as add-on therapy to a xanthine oxidase inhibitor.\textsuperscript{16} In large, randomized clinical trials, lesinurad in combination with either allopurinol or febuxostat has demonstrated greater efficacy than either of the xanthine oxidase inhibitors as monotherapy (TABLE).\textsuperscript{18,19,22-25} Lesinurad has been associated with a transient elevation of serum creatinine and kidney stones, the incidence of which is higher if taken without a xanthine oxidase inhibitor.

Pegloticase can be considered in patients with crystal-proven severe, debilitating chronic tophaceous gout and poor QoL, in whom the sUA target level cannot be reached with any other available drug at the maximal dosage (including combination therapy).\textsuperscript{12} Pegloticase is an IV medication that must be given at an appropriately trained infusion center because there is a risk of anaphylaxis.

The TABLE summarizes results of key clinical trials for ULT agents approved in the United States.\textsuperscript{18,19,22-25}

**HOW IS EACH OF THE APPROVED URATE-LOWERING MEDICATIONS INITIATED AND TITRATED?**

A treat-to-target approach should be utilized, whereby ULT is initiated and intensified as needed to achieve and maintain the target sUA level <6 mg/dL, or ≤5 mg/dL in certain patients (eg, those with tophi), as discussed.\textsuperscript{12,15} Because initiation of ULT is associated with gout flares for approximately the first 6 months, prophylactic use of anti-inflammatory therapy (eg, colchicine or a nonsteroidal anti-inflammatory drug) is recommended during that time frame.\textsuperscript{13}

**Allopurinol**

In patients with normal kidney function, allopurinol is initiated at a low dosage (100 mg/d) and increased by 100 mg/d increments every 2 to 4 weeks if required, to reach the uricemic target.\textsuperscript{12} A reduced initial dose, eg, 50 mg/d, and a daily dose of 200 mg is suggested in patients with a creatinine clearance of 10 to 20 mL/minute. This approach can minimize the risk of a severe cutaneous hypersensitivity reaction (eg, Stevens-Johnson syndrome) as well as an acute gout flare.\textsuperscript{15} In approximately 30% to 50% of patients with normal kidney function, 300 mg/d is the most commonly used dosage of allopurinol. Because 300 mg/d does not achieve the target sUA level of <6 mg/dL in more than 50% of patients with gout, guidelines recommend dosage escalation when needed to reach the sUA target.\textsuperscript{15} Dosages of 600 to 800 mg/d have a 75% to 80% success rate in achieving an sUA level <6 mg/dL.\textsuperscript{12} Dosages >300 mg/d are given in divided doses to avoid gastrointestinal side effects. In patients with renal impairment, EULAR guidelines recommend adjusting the allopurinol dosage downward due to the risk of serious cutaneous adverse events.\textsuperscript{12} ACR guidelines, however, recommend increasing allopurinol until the sUA target level is reached in these patients, while monitoring for drug toxicity.\textsuperscript{15} The ACR recommendation is based on several small series of patients in which no increased incidence of severe reactions was demonstrated in patients whose allopurinol dosages were progressively titrated above those recommended, based on creatinine clearance and the level of renal impairment.\textsuperscript{6,18,19,26-28}

**Febuxostat**

Febuxostat is approved by the FDA at a starting dosage of 40 mg/d, uptitrated to 80 mg/d if patients do not achieve an sUA level <6 mg/dL after 2 weeks.\textsuperscript{20} ACR guidelines suggest uptitration to as much as 120 mg/d (an investigational dosage) if necessary to achieve the target sUA level.\textsuperscript{15}

**Probenecid**

The initial dosage of probenecid is 250 mg twice daily, uptitrated weekly to 1 g twice daily, based on the sUA level.\textsuperscript{6} Patients must be counseled to hydrate well due to the risk of urolithiasis.\textsuperscript{15} Probenecid is not recommended for patients with a creatinine clearance <50 mL/min, due to lack of data on long-term safety and efficacy in stage 3 CKD.\textsuperscript{15}

**Lesinurad**

Lesinurad is indicated at a dosage of 200 mg/d as add-on therapy to allopurinol or febuxostat.\textsuperscript{16} Lesinurad should not be initiated in patients with a creatinine clearance <45 mL/min; renal function should be evaluated prior to initiation and periodically thereafter.\textsuperscript{16} Lesinurad is available as a 200 mg tablet and as a combination tablet of
200 mg of lesinurad with either 200 mg or 300 mg of allopurinol, which may improve patient adherence and lessen the risk of lesinurad being inadverntly taken without allopurinol.16,29

Pegloticase
Pegloticase must be administered under supervision at an infusion center, due to the high risk of serious allergic reaction, including anaphylaxis.30 Pegloticase is administered as an 8-mg IV infusion every 2 weeks, and should not be combined with urate-lowering medications.30

CASE STUDY, HARRIET (CONTINUED)
Because Harriet has not reached the sUA target of <6.0 mg/dL and she is tolerating allopurinol, the decision is made to increase the dosage of allopurinol to 200 mg twice daily and recheck the sUA level in 2 weeks.

SUMMARY
Gout is a common disorder that is associated with significant patient morbidity, as well as with comorbidities such as CKD, diabetes, and various cardiovascular disorders. Diagnosis is often based on history and physical examination, with confirmation by joint aspiration when necessary. Lifestyle management generally provides modest reduction of the sUA level. Several urate-lowering medications have been approved for chronic therapy. Allopurinol is typically used as first-line therapy. When combination therapy is required to achieve the target sUA level, the choice is generally based on patient-specific factors, physician and patient choice, and cost.
exist in clinical practice. To aid in the optimal management of elevated LDL-C levels, medical associations have developed guidelines or recommendations with a focus on patient-centric care (TABLE 1).1-4

A key challenge for any target condition is individual risk assessment of patients for primary prevention. Performing risk scoring to estimate 10-year atherosclerotic cardiovascular disease (ASCVD) risk helps stratify patients in determining appropriate lipid targets and statin intensity. Most notable is the American College of Cardiology (ACC) ASCVD risk estimator,1 which recommends moderate- to high-intensity statin (TABLE 2) therapy for those with 10-year ASCVD risk of ≥7.5%. Such recommendations align with the general principles that the intensity of risk-reduction therapy should be adjusted to the patient’s absolute ASCVD risk and that the benefit of risk reduction is proportional to the extent of LDL-C reduction.1,2 Moreover, limited data exist on managing certain complex populations. For example, individuals with human immunodeficiency syndrome (HIV) have inherently high CV risk, yet remain understudied.

Three decades of statin data and guideline revisions have shown how critically important it is to take a patient-centric approach by individualizing treatment so as to improve adherence and, ultimately, patient care.

DIFFERENTIATING AMONG STATINS

Effectiveness in LDL-C lowering

It is imperative to assess individual patient characteristics and needs when prescribing statins. Selecting among the statins, as well as the statin dose, requires the clinician to find the “best fit” to limit adverse effects (AEs), improve long-term adherence, and ultimately reduce ASCVD events. A key differentiation among the statins is their effectiveness in lowering LDL-C, with dose intensity based on desired percent LDL-C reduction (TABLE 2) and corresponding to the overall 10-year ASCVD risk.1,2 In general, moderate- to high-intensity statins are recommended for patients with a 10-year ASCVD risk score ≥7.5% or who have previously experienced a CV event. Moderate-intensity statins can also be considered for patients with a 10-year ASCVD risk score of 5% to <7.5%. Moderate-intensity statins result in a 30% to <50% reduction in LDL-C, whereas high-intensity agents reduce LDL-C by ≥50%. The National Lipid Association (NLA) also stresses the importance of non-high-density lipoprotein cholesterol
(non-HDL-C) and LDL-C, both of which are considered the root cause of atherosclerosis. Consequently, the NLA recommends both as primary targets of therapy (TABLE 1).

Although the non-HDL-C target is 30 mg/dL higher than the LDL-C goal, non-HDL-C reduction is typically proportional to statin intensity and achieved LDL-C reduction.

Importantly, the American College of Cardiology/American Heart Association (ACC/AHA) notes numerous intensity-modifying factors that can be considered for those who are otherwise candidates for a high-intensity statin. These include patients with multiple or serious comorbidities such as impaired renal or hepatic function, a history of statin intolerance or muscle disorders, unexplained liver function test (LFT) elevations, concomitant drug interactions (DIs), age >75 years, and Asian ancestry. In such patients, moderate-intensity statin therapy may be a better choice for overall safety and tolerability.

### STATIN SAFETY

Treatment safety and patient tolerability are key considerations in developing a treatment plan. Differences among the statins provides an opportunity to individualize therapy and give patients the best chance of staying on lifelong treatment to prevent ASCVD. When safety or tolerability issues preclude continued use of one statin, switching to another statin with attributes that are aligned with the individual patient should be considered before leaving the statin class for other lipid-modifying agents. For example, switching to a statin with low potential for DIs in a patient with polypharmacy limits safety concerns and the likelihood of concentration-dependent AEs.

### Safety and tolerability

Although numerous factors can affect statin safety and tolerability, statins have an overall favorable safety profile. Severe
AEs resulting in hospitalizations (ie, rhabdomyolysis) are very rare with an estimated annual incidence of 0.44 per 10,000 person-years with statin monotherapy. Safety and tolerability are important considerations for statin therapy since, whether real or perceived, AEs are the primary reason for statin discontinuation. This is important since statin discontinuation is associated with higher rates of ASCVD. Statin safety and potential AEs are common topics in the medical literature and mainstream media. As such, the US Food and Drug Administration (FDA) and the NLA have provided updates including potential risks of statin use.

When statin therapy results in a major AE, an underlying DI is frequently implicated. Drug interactions are well established with the individual statins. Most worrisome are concomitant medications that may increase statin levels by several-fold, resulting in concentration-dependent AEs (FIGURE) (see Drug Interactions on page S46). Those with advanced age are perhaps most at risk for DIs due to polypharmacy and comorbidities, and AEs may be most debilitating in patients age ≥65 years.

**Statin intolerance**

One limitation of statin therapy is statin intolerance. Although there is no universally agreed upon definition, the NLA defines statin intolerance as “adverse symptoms, signs, or laboratory abnormalities attributed by the patient (or provider) to the statin and in most cases perceived by the patient to interfere unacceptably with activities of daily living, leading to a decision to stop or reduce statin therapy” (see Drug Interactions on page S46). Those with advanced age are perhaps most at risk for DIs due to polypharmacy and comorbidities, and AEs may be most debilitating in patients age ≥65 years.

**Muscle-associated symptoms or injury**

The primary barrier to statin therapy is patient-reported musculoskeletal complaints. The clinical presentation of SAMS is highly subjective, as CK levels are typically normal, and involves a spectrum of symptoms, which overlap with common musculoskeletal conditions. Moreover, SAMS negatively impacts outcomes as discontinuation or down-titration of statin therapy is associated with higher rates of ASCVD. Various tools and approaches have been developed to determine if symptoms are statin-related and to assist with management.

One such tool is the Statin Myalgia Clinical Index (SMCI), which has recently been revised. Key features of the SMCI suggesting statin etiology include symmetric distribution of unexplained muscle symptoms, symptom onset shortly after initiation, improvement within 2 weeks after dechallenge, and symptom reoccurrence within 4 weeks of rechallenge. If the symptoms are determined to be statin-related, numerous approaches can be utilized including trying a different statin, implementing an alternate dosing strategy (such as once-weekly dosing) with a statin that has a long half-life (ie, atorv-
Hepatotoxicity

The potential for hepatotoxicity with lipid-altering agents has historically been a concern for clinicians and, more recently, patients. However, in 2012, the FDA removed the need for routine periodic monitoring of hepatic enzymes in all statin labeling. Instead, the FDA recommended that LFTs only need to be performed prior to initiating statin therapy, and as clinically indicated thereafter.

Statins have been implicated in cases of severe hepatotoxicity, but the incidence is exceedingly rare. A population-based study evaluated the incidence of hospitalization due to drug-induced acute liver failure among ~5.5 million patients. Of 32 cases identified over a 6-year period, nearly 80% implicated either acetaminophen or dietary supplements, while two involved statin therapy, along with other concomitant agents. For managing potential statin-associated hepatotoxicity, repeating LFTs to confirm persistent elevations and using sound clinical judgment are the most critical.

**CASE SCENARIO #1**

JS is a 63-year-old male being seen for a follow-up visit. He has been taking simvastatin 20 mg/day for the past year; LDL-C is now 105 mg/dL. At last visit 3 months ago, he was started on verapamil for hypertension, which is now controlled. His 10-year ASCVD risk score is 16.6%, but he is otherwise healthy. Today, he is complaining of achy muscles that make it hard for him as a custodian at a local school. JS notes that he is not sure he wants to continue statin therapy and is uncertain whether he really needs it.

**DRUG INTERACTIONS**

A key step to individualizing statin therapy is awareness of potential DIs. Multiple steps are involved in statin metabolism. In addition to the well-described cytochrome P450 (CYP) enzyme system, numerous drug transporters are involved in statin metabolism, including multidrug-resistant-associated proteins, breast cancer-resistant proteins, P-glycoproteins, and organic anion-transporting polypeptides (OATPs), particularly OATP1B1. Statins are potential substrates for such pathways, but the affinity for specific transporters and CYP450 isoenzymes vary greatly among medications. Several commonly prescribed medications can interfere with one or more of the transporters or enzymatic pathways, and markedly increase statin serum concentrations and the risk for statin-related AEs.
for their metabolism are pitavastatin and pravastatin and thus, may have a reduced potential for significant DIs.\textsuperscript{12}

**CASE SCENARIO #1 (CONTINUED)**

This case presents a common scenario in which a DI may have occurred with the addition of verapamil to simvastatin, which may have contributed to the patient’s subsequent hesitancy to continue statin therapy. It also underscores the patient’s limited understanding of his ASCVD risk. Discussing his 10-year risk score can be used to improve his understanding and hopefully motivate him to agree to further treatment for his elevated LDL-C. Verapamil could be discontinued and the patient switched to another antihypertensive medication that is not metabolized via CYP3A4. If this is done, the dose of simvastatin should be increased to provide additional LDL-C reduction. Alternatively, the simvastatin could be discontinued and the patient switched to another statin that is not metabolized via CYP3A4 at a dose that would provide additional LDL-C reduction.

Another key metabolic step with statins is hepatic uptake with OATPs, especially OATP1B1.\textsuperscript{12} All statins are substrates for OATP1B1 (\textbf{Figure}). Common inhibitors of OATP1B1 include cyclosporine, erythromycin, and gemfibrozil. Cyclosporine not only inhibits OATP1B1 but other statin metabolic pathways and may increase statin concentrations several-fold. As such, cyclosporine should generally be avoided with statins. Although statin concentrations are only modestly increased (1-2-fold) with gemfibrozil, concomitant use of statins and gemfibrozil should be avoided or recommended dose limits should be followed for certain agents.\textsuperscript{12}

**CASE SCENARIO #2**

MR is a 46-year-old male presenting for follow-up. His past medical history is significant for HIV, poorly controlled type 2 diabetes mellitus (DM), hypertension, atrial fibrillation, and depression. Other notable information is a family history of premature ASCVD, current tobacco use (1 pack/day), no alcohol intake, and a 10-year ASCVD risk score of 24%. MR reports no recent hospitalizations but admits that he is concerned regarding his future health, given his HIV status and family history of early ASCVD. Current labs indicate a mixed dyslipidemic pattern with an LDL-C of 110 mg/dL; C-reactive protein is moderately elevated. Medications of interest include his HIV protease inhibitors lopinavir + ritonavir, amlodipine, warfarin, but no antihyperlipidemic agents.

Certain populations are prone to DIs and potential statin-related AEs. These include patients taking multiple medications or conditions requiring complex drug regimens such as HIV infection and solid organ transplants.\textsuperscript{7} For those with HIV and taking protease inhibitors, the FDA has provided guidance on the use of statins to limit DIs.\textsuperscript{19} Most statins have dose limits (rosuvastatin, atorvastatin), are contraindicated (lovastatin, simvastatin), have no data available (fluvastatin), or should be avoided with certain HIV protease inhibitors (atorvastatin). Conversely, pitavastatin and pravastatin have no dose limits or additional precautions with concomitant use of HIV protease inhibitors. The HIV population is also at significant risk for ASCVD secondary to HIV, comorbid dyslipidemia, and chronic inflammation. Epidemiologic data indicate that those with HIV infection have a 2-fold increased rate of CV events relative to non-infected patients.\textsuperscript{20} To best answer the question of the benefit of statins in preventing ASCVD in this understudied population at high risk for ASCVD, the National Institute of Allergy and Infectious Diseases and Division of AIDS is currently conducting a landmark outcome trial comparing the effects of pitavastatin versus placebo on composite CV events (REPRIEVE).\textsuperscript{21}

**CASE SCENARIO #2 (CONTINUED)**

MR is an example of a patient with significant ASCVD risk and requiring a complicated medication regimen. His 10-year ASCVD risk score of 24% may be underestimated since most risk calculators do not factor in premature family history of ASCVD and inflammatory measures,\textsuperscript{1,2} nor do they factor in HIV infection. The clinician must recognize the need for statin therapy and the need to stop smoking, but also be aware of the potential for major DIs and severe AEs. Given his ASCVD risk, implementing a safe, moderate-intensity statin for LDL-C reduction of 30% to 49% may be considered.

Clinicians must understand statin-related DIs, especially among populations requiring complex drug regimens. It is imperative to avoid critical combinations of the statins most prone to DIs (ie, lovastatin, simvastatin, atorvastatin) with specific agents having the highest potential for increasing statin concentrations (eg, azole antifungals, macrolides, cyclosporine, gemfibrozil, HIV protease inhibitors). Further, certain statins (eg, rosuvastatin, simvastatin) inhibit warfarin clearance, thus increasing the potential for bleeding during statin treatment initiation.\textsuperscript{12} Awareness of such interactions may limit statin-related AEs and potentially improve adherence and long-term outcomes.

**New onset diabetes**

Consistent with earlier observations, a small but significant association between new onset diabetes (NOD) and rosuvastatin therapy was observed in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study.\textsuperscript{22} A subsequent meta-analysis confirmed this small but significant link as statin therapy was associated with a 9% increased risk for incident DM.\textsuperscript{23} An additional analysis by Preiss et al evaluated statin dose and
determined that high-dose statin therapy was associated with a 12% greater likelihood of NOD compared to moderate dose therapy. In 2013, a comprehensive meta-analysis further confirmed a dose-dependent link with NOD and a gradient of risk across many different individual statins. Overall, most data indicate a modest increase in NOD (10%-12%) with several statin therapies, particularly among those at risk for DM.

In terms of number needed to harm, one meta-analysis of randomized controlled trials (RCTs) (N=91,140) found that treating 255 patients with statin therapy for 4 years would yield one additional case of DM. Conversely, a few observational studies note higher rates and a stronger correlation, suggesting that de-prescribing statin therapy in certain populations (i.e., women age >75 years) may be advisable.

The FDA considers statin-associated NOD a class effect, but most data suggest the link is secondary to dose and each statin. Zaharan et al found significantly higher rates of NOD with atorvastatin (HR, 1.25; 95%CI, 1.02–1.55) and simvastatin (HR, 1.14; 95%CI, 1.00–1.00) compared to pravastatin (HR, 1.02; 95%CI, 0.98–1.06) and fluvastatin (HR, 1.04; 95%CI, 0.90–1.21).

A meta-analysis of pitavastatin RCTs, including doses up to 8 mg daily, found no adverse effect on glucose metabolism or NOD.

**Cognition**

Limited data have suggested an association between statins and cognitive impairment (CI), prompting labeling changes to all statins in 2012. The FDA indicated that post-marketing AE reports... described individuals over the age of 50 who experienced notable, but ill-defined memory loss or impairment that was reversible upon discontinuation of statin therapy.

The FDA stressed the rarity of these events and that there is no evidence to indicate progression to dementia. At worst, a weak causal effect is suggested. Conversely, other data have suggested a neutral or protective effect on cognition with statin therapy.

For example, an analysis of a possible association between statins and Alzheimer’s disease among Medicare beneficiaries (N=399,979) showed that patients with high statin exposure had a significantly lower risk of developing Alzheimer’s disease (HR, 0.65-0.88; P<0.01) compared to those with minimal statin exposure.

Overall findings involving statin therapy and cognitive effects are mixed. If statin associated CI is suspected, ruling out other causes is warranted. If symptoms persist following statin discontinuation, neuropsychological testing can be considered.

**SUMMARY**

Statins are endorsed as first-line therapy by numerous authorities for LDL-C reduction and prevention of ASCVD. For optimal management, statin intensity should provide the LDL-C reduction needed based on the patient’s overall ASCVD risk. Statins possess a favorable safety profile, yet musculoskeletal complaints are a major barrier, often resulting in discontinuation of statin therapy. Certain statins are prone to significantly more severe DIs based on metabolism and can result in dose-dependent AEs. Clinicians must be aware of these factors to appropriately individualize therapy for optimal patient outcomes.

**REFERENCES**


INTRODUCTION
Despite a greater understanding of pathophysiologic processes of type 2 diabetes mellitus (T2DM) and new classes of medications targeting these processes, the treatment of persons with T2DM remains a formidable challenge. Recent evidence suggests that one-third to one-half of patients with T2DM have not achieved target glycemic control, that is, a glycated hemoglobin (A1c) <7%.1,2 A key reason appears to be a low rate of timely treatment intensification. Among patients with A1c >7% on metformin monotherapy, recent data indicate that only 38% had evidence of addition of a second glucose-lowering medication during the subsequent 12 months.3

Patients treated with basal insulin fare no better. Blonde et al found that 19% achieved A1c control 6 months after initiating basal insulin therapy and 31% after 12 months.4 Other investigators showed that after initiation of basal insulin, an A1c level ≤7% was achieved in 21% to 27% of patients at 3 months and 28% at 24 months.5,6 Individuals who do not have early treatment intensification are less likely to have any treatment intensification at all. For example, failure to achieve A1c ≤7% at 3 months was found to be associated with an increased risk of failing to achieve the A1c target at 24 months (odds ratio [OR] 3.7; 95% confidence interval [CI], 3.41-4.0).8 Recent evidence indicates that in patients with inadequate glycemic control taking basal insulin, treatment intensification with prandial or premix insulin or a glucagon-like peptide-1 receptor agonist (GLP-1RA) took an average 4.3 years and happened in 31% of eligible patients.7

In patients treated with basal insulin, markers indicating the need to consider additional therapy include (1) an elevated A1c and persistent postprandial hyperglycemia despite a normal or near-normal fasting plasma glucose (FPG) concentration; (2) a total daily dose of basal insulin >0.5 units/kg; (3) severe, nocturnal, or frequent symptomatic hypoglycemia; and (4) persistent difference between bedtime and before-breakfast blood glucose >55 mg/dL.8,9 An even lower total daily dose of basal insulin as a marker for dose intensification has been suggested by a post hoc analysis of 3 insulin glargine titration studies of at least 24 weeks' duration (N=458).10 The analysis found that reduction in the FPG begins to slow at ~0.3 units/kg, leveling at ~0.5 units/kg.

These findings are a concern and emphasize the importance of staying ahead of this progressive disease through timely, individualized treatment intensification. Recommendations for intensifying glycemic control over time vary between the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE), although both recommend using a patient-centric approach to treatment and intensifying every 2 to 3 months.8,11 The 2018 ADA/EASD guideline recommends a sequential approach to treatment, generally beginning with metformin monotherapy.8 If the A1c target is not achieved after 3 months of metformin monotherapy, and adherence is assured, treatment should be intensified based on patient factors, including cardiovascular risk. Options include sodium-glucose cotransporter-2 inhibitors (SGLT-2is), GLP-1RAs, dipeptidyl peptidase-4 inhibitors (DPP-4is), thiazolidinediones (TZDs), sulfonylureas, and basal insulin. For patients with A1c ≥10%, blood glucose ≥300 mg/dL, or markedly symptomatic, combination injectable therapy (basal insulin in combination with a GLP-1RA or prandial insulin) should be considered.

In contrast, the 2018 AACE/ACE guideline stratifies therapy based on A1c (<7.5%, 7.5%-9%, >9%).11 The AACE/ACE guideline recommends the following hierarchy of usage...
for addition to metformin monotherapy: GLP-1RA, SGLT-2i, DPP-4i, TZD, basal insulin, and others. Each of these classes of agents has benefits and limitations to be considered when individualizing treatment. For patients with A1c >9%, basal insulin alone or in combination with other agents should be used if the patient is symptomatic; if not, metformin-based dual or triple therapy should be considered. No matter the treatment chosen, the treatment plan should be assessed every 2 to 3 months and treatment intensified if target glucose goals are not achieved. The remainder of this article will discuss the use of basal insulin and GLP-1RAs, focusing on their combined use.

EFFECTS OF BASAL INSULIN AND GLP-1RAs ON THE GLYCEMIC PROFILE

Long-acting basal insulins are intended to reduce the FPG level by mimicking the nonmeal secretion of insulin over the 24-hour day, which in turn suppresses hepatic glucose production. This mechanism of action is in contrast to bolus or prandial insulins, which are intended to lower the postprandial rise in glucose level after nutrient ingestion. People who are using insulin alone for the treatment of their diabetes will often need both insulin components for target glucose control. However, the use of basal insulin is much more common than mealtime insulin in primary care for the treatment of patients with T2DM. If basal insulin at a daily dose ≥0.5 units/kg is needed to normalize the FPG, close blood glucose monitoring is advised because of an increasing risk of hypoglycemia, especially if a meal is missed or a person is more active on a given day.

A key feature of the GLP-1RAs is their ability to stimulate insulin secretion and suppress glucagon secretion, both in a glucose-dependent manner, thus exerting greater effect when the blood glucose level is elevated and minimal effect as the blood glucose level approaches normal, thereby reducing the risk of hypoglycemia. The long-acting GLP-1RAs (albiglutide, dulaglutide, exenatide once-weekly, liraglutide, and semaglutide), which have a greater effect on stimulating insulin secretion and inhibiting glucagon secretion, produce strong reduction of FPG and modest reduction of postprandial glucose (PPG).

The short-acting GLP-1RAs (exenatide twice-daily and lixisenatide), which slow gastric emptying, produce strong reduction of PPG and modest reduction of FPG. The GLP-1RAs also suppress appetite, producing modest weight loss of 1 to 2 kg in most patients with T2DM.

EARLY USE OF BASAL INSULIN AND GLP-1RAs

Among the attributes of an ideal medication for T2DM is the ability to achieve and maintain long-term glycemic-lowering effectiveness. The early addition of basal insulin to metformin improves glycemic control and lowers the risk of hypoglycemia compared with later addition of a sulfonylurea to metformin. Moreover, as a natural hormone, insulin is effective long-term, with the magnitude of glycemic lowering dependent on dose and limited by the risk of hypoglycemia.

The GLP-1RAs serve to normalize the impaired incretin effect observed in patients with T2DM, providing an additional 0.5% to 1.3% A1c lowering when added to metformin. Clinical investigation shows that GLP-1RAs improve various markers of beta-cell function, including homeostatic model assessment of β-cell function (HOMA-B), thus suggesting long-term effectiveness. Further support for long-term glycemic effectiveness for GLP-1RAs stems from a network meta-analysis of 301 clinical trials (118,000 patient-years of treatment). The analysis yielded an intermediate OR for treatment failure for a GLP-1RA in combination with metformin. Treatment failure was defined as lack of efficacy or need for additional glucose-lowering therapy. Using the sulfonylureas as the reference class (treatment failure OR = 1), the order of treatment failure (ORs least to greatest) was estimated to be basal insulin (0.1); SGLT-2i (0.68); GLP-1RA (0.84); sulfonylurea (1); TZD (1.18); and DPP-4i (1.37).

COMBINATION OF BASAL INSULIN WITH A GLP-1RA

As suggested above, patients who do not achieve adequate A1c control despite basal insulin therapy often have postprandial hyperglycemia. Historically, to normalize the PPG, rapid- or short-acting prandial insulin has been added to basal insulin. Although generally effective in improving postprandial hyperglycemia and achieving A1c <7%, the addition of prandial insulin to basal insulin is often limited by weight gain and more frequent symptomatic hypoglycemia. Further, prandial insulin is a dosing challenge unless the person is willing to be carbohydrate consistent. Otherwise, matching the dose with food intake is difficult. In addition, the general need for multiple injections per day usually requires people to carry their “diabetes supplies” with them to work, school, or eating out. This can be a substantial burden that adversely affects patient adherence.

In contrast, the complementary glycemic effects of a GLP-1RA with basal insulin, coupled with their low incidence of hypoglycemia and their weight-loss effects, provide a strong rationale for using a GLP-1RA in place of prandial insulin for use in combination with basal insulin. They can be taken less often (twice daily to once weekly) and often do not need to be taken outside the home.

Comparison of GLP-1RA vs prandial insulin

Diamant et al compared a GLP-1RA vs prandial insulin, both in combination with basal insulin and metformin. After a 12-week period to optimize the dose of insulin glargine
Patients treated for 12 to 52 weeks. Compared with patients decreased in occurrence with continued dosing. The most commonly reported adverse events were gastrointestinal without weight gain or an increased risk of hypoglycemia. Weight loss was commonly observed. The addition of a GLP-1RA with insulin improved glycemic control with or without prandial insulin. Across the 19 studies, the combination of basal insulin and GLP-1RA had significantly greater reductions in A1c (weighted mean difference [WMD], -0.47%; 95% CI, -0.59 to -0.35) and body weight (WMD, -2.5 kg; 95% CI, -3.3 to -1.7 kg), were more likely to achieve the A1c target (relative risk [RR], 1.65; 95% CI, 1.44-1.88), and had similar rates of hypoglycemia (RR, 1.14; 95% CI, 0.93-1.39).

Combination of insulin with a GLP-1RA
The complementary glycemic and nonglycemic effects of basal insulin and GLP-1RAs provide a strong rationale for their combined use. The benefits of the combination were demonstrated by a systematic review of 14 observational/real-world studies and 5 clinical trials involving approximately 5000 patients with T2DM for 7 to 15 years and treated with the combination of GLP-1RA and basal insulin with or without prandial insulin. Across the 19 studies, the combination of a GLP-1RA with insulin improved glycemic control without weight gain or an increased risk of hypoglycemia. Weight loss was commonly observed. The addition of a GLP-1RA to basal insulin therapy allowed for a reduction of the total daily insulin dose without a loss of glucose control. The most commonly reported adverse events were gastrointestinal, but were generally mild or moderate in severity and decreased in occurrence with continued dosing.

Similar results were reported in a more recent meta-analysis of 26 randomized clinical trials involving 11,425 patients treated for 12 to 52 weeks. Compared with patients treated with a variety of regimens consisting of basal insulin with or without prandial insulin, patients treated with the combination of basal insulin and GLP-1RA had significantly greater reductions in A1c (weighted mean difference [WMD], -0.47%; 95% CI, -0.59 to -0.35) and body weight (WMD, -2.5 kg; 95% CI, -3.3 to -1.7 kg), were more likely to achieve the A1c target (relative risk [RR], 1.65; 95% CI, 1.44-1.88), and had similar rates of hypoglycemia (RR, 1.14; 95% CI, 0.93-1.39).

Fixed-ratio combination products of basal insulin and GLP-1RA
The glycemic and nonglycemic benefits observed with the combination of basal insulin and a GLP-1RA as individual medications led to the development of fixed-ratio combination products. An advantage of these combination products for patients is that they avoid the need for 2 separate injections and 2 copays.

One fixed-ratio product combines insulin glargine U-100 with lixisenatide (IGlarLixi) and the other combines insulin degludec U-100 with liraglutide (IDegLira). Both products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on basal insulin or GLP-1RA therapy. Both are titrated based on the basal insulin component, allowing for a slow increase in the GLP-1RA dose, thereby minimizing the frequency and severity of nausea and vomiting. IGlarLixi can be titrated over the range of 15 to 60 units, in which 1 unit of IGlarLixi equals 1 unit of glargine and 0.33 mcg of lixisenatide. The maximum dose of lixisenatide is 20 mcg. IDegLira can be titrated over the range of 10 to 50 units, in which 1 unit of IDegLira equals 1 unit of degludec and 0.036 mg of liraglutide. The maximum dose of liraglutide is 1.8 mg. Both are available only in pen devices.
patients in the lixisenatide group. No cases of pancreatitis occurred.37

**LixiLan-L trial**
The LixiLan-L trial compared IGlarLixi with up-titrated glargine U-100 in patients who had inadequate glycemic control while using glargine 15 to 40 units/d plus oral agents (N=736).38 After a 6-week run-in during which oral agents other than metformin were stopped, patients were treated for 30 weeks with doses of IGlarLixi and up-titrated glargine capped at 60 units/d. From a baseline A1c of 8.1%, the A1c was reduced -1.1% in the IGlarLixi group and -0.6% in the glargine group (P<.0001). A post hoc analysis demonstrated that the reductions in A1c were greater for IGlarLixi than glargine for each of 3 groups of patients based on screening A1c level (A1c ≤8%, 8%-9%, and >9%) (all P<.0001).39

Although the reduction in FPG was small (-7 mg/dL with IGlarLixi and -9 mg/dL with glargine), the PPG reduction was significantly greater with IGlarLixi than glargine (-85 vs -25 mg/dL, respectively; 95% CI, -3.9 to -2.8). The mean final total daily dose of insulin was 47 units in both groups.

More patients in the IGlarLixi group than the glargine group achieved several composite endpoints that consisted of glycemic control, no weight gain, and/or no hypoglycemia. These benefits were independent of baseline A1c, body mass index, and duration of T2DM.40,41 For example, 20% of IGlarLixi patients at a median of 153 days, but was never reached by 50% of patients with glargine.42 In patients treated with IGlarLixi in LixiLan-O, the change from baseline in PPG excursion was -29, -36, and -52 mg/dL for the lixisenatide dose groups of 5 to 10, 10 to 15, and 15 to 20 mcg, respectively.43 Glycemic and nonglycemic outcomes with IGlarLixi have been found to be generally similar in patients ≥65 years of age compared with patients <65 years, with no increased risk of hypoglycemia.44 Modest weight loss was observed in patients ≥65 years of age.

**INSULIN DEGLUDEC/LIRAGLUTIDE**

**DUAL-I trial**
The DUAL-I trial compared the individual components of degludec U-100 and lixisenatide 1.8 mg/d with the fixed-ratio product IDEgLira in patients with T2DM inadequately controlled with metformin with or without pioglitazone (N=1660).45 Patients were treated for 26 weeks, after which approximately three-quarters of patients continued treatment for an additional 26 weeks. After 52 weeks, from a baseline A1c of 8.3%, the A1c reduction was greatest with IDEgLira than degludec or lixisenatide (1.8% vs 1.4% vs 1.3%; both P<.0001 vs IDEgLira). The reduction in FPG was similar with IDEgLira (-62 mg/dL) and degludec (-61 mg/dL), and smaller with lixisenatide (-30 mg/dL; P<.0001 vs IDEgLira). The total daily dose of insulin at study end was 39 units with IDEgLira and 62 units with degludec. Substudy analysis showed the decrease in the PPG increment was similar with IDEgLira and lixisenatide, both of which were greater than with degludec.46

Changes in body weight were as expected, with a -0.4 kg loss with IDEgLira. The rate of confirmed hypoglycemia (requiring assistance or <56 mg/dL with or without symptoms) was highest with degludec (2.6 events/patient-year) and least with lixisenatide (0.2 events/patient-year). Nausea occurred less frequently with IDEgLira than lixisenatide (9% vs 20%), likely because of the slow increase in lixisenatide dose due to titration of the insulin dose. A positively adjudicated major adverse cardiovascular event occurred in 4 patients in the IDEgLira group and 1 in each of the degludec and lixisenatide groups. Two cases of treatment-emergent pancreatitis occurred in the lixisenatide group, but were judged as unlikely to be treatment-related.

**DUAL-II trial**
The DUAL-II trial compared IDEgLira with degludec, both once daily with the maximum degludec dose capped at 50 units.47 Patients (N=413) had inadequate glycemic control despite basal insulin 20 to 40 units/d in combination with metformin with or without a sulfonylurea or meglitinide. At randomization to IDEgLira or degludec, patients were continued on metformin alone. Insulin doses were titrated to achieve a FPG of 72 to 90 mg/dL. After 26 weeks, from a baseline A1c of 8.7% to 8.8%, the A1c was reduced -1.9% in the IDEgLira group and -0.9% in the degludec group (P<.0001). Similarly, the FPG reduction was greater with IDEgLira than with degludec (-62 vs -46 mg/dL, respectively; P=.0019). The 2-hour PPG excursion was similar (40 vs 43 mg/dL, respectively). The mean total daily degludec dose was 45 units in each group.

More patients in the IDEgLira group than the degludec group achieved several composite endpoints that consisted of glycemic control, no weight gain, and/or no hypoglycemia. The rates of confirmed and nocturnal hypoglycemia were similar in both groups. Similar to DUAL-I, nausea occurred more frequently with IDEgLira than with degludec (6.5% vs 3.5%). One positively adjudicated major adverse cardiovas-
cular event occurred with IDegLira and 2 with degludec. No cases of pancreatitis were observed.

Post hoc analyses
Further analyses of DUAL-I and DUAL-II and other DUAL trials have provided additional insight regarding the benefits of IDegLira compared with degludec. As expected, the magnitude of A1c lowering increased with increasing A1c at baseline.48 However, A1c reductions with IDegLira were significantly greater than with degludec or liraglutide in all baseline A1c categories (P<.01) (≤7.5%, >7.5%-8.5%, >8.5%-9%, >9%), except for no difference in the lowest A1c category in DUAL-II. The DUAL-V trial, which compared IDegLira with glargine, also showed IDegLira to be significantly more effective than glargine for reducing A1c across all baseline A1c categories (P<.0001) (≤7.5%, >7.5%-8.5%, >8.5%).49 Similarly, IDegLira was significantly more effective than glargine for reducing A1c irrespective of baseline FPG (P<.0001) (<130 and ≥130 mg/dL) or body mass index (P<.0001) (<30, 30 to <35, and ≥35 kg/m²).

Additional analysis of DUAL-I and DUAL-II showed the mean A1c to be significantly lower and the proportion of patients achieving A1c <7% significantly greater at weeks 8 and 12 with IDegLira (all P<.0001).50 Reductions in A1c also have been shown to be significantly greater with IDegLira vs comparators (basal insulin, GLP-1RA, placebo) in patients with mildly or moderately impaired renal function (estimated glomerular filtration rate ≥90, ≥60 to <90, ≥30 to <60 mL/min/1.73 m²).51

In DUAL-I, a subset of patients underwent continuous glucose monitoring after meal tests.46 Results showed a reduction in the PPG increment after all 3 main meals. The reduction was similar for IDegLira and liraglutide, both significantly greater than for degludec. Additional data suggested that the improvement was partially explained by higher endogenous insulin secretion and improved β-cell function due to liraglutide.

The data from DUAL-I, as well as 9-point self-monitored blood glucose (SMBG) profiles from DUAL-I and DUAL-II, showed that IDegLira resulted in a higher proportion of patients with SMBG values within the target range (70-162 mg/dL) for all pre- and postprandial values, as well as for the full 9-point profile (P<.01 for all).52 Moreover, reduction in the fluctuation of interstitial glucose was significantly greater with IDegLira than liraglutide (P=.0072).

**DOSING AND TITRATION**
Before initiating IGlarLixi or IDegLira, basal insulin and GLP-1RA therapy must be discontinued.53 IGlarLixi is initiated at a dose of 15 units (15 units glargine and 5 mcg lixisenatide) for patients taking basal insulin <30 units/d or taking lixisenatide, or at a dose of 30 units (30 units glargine and 10 mcg lixisenatide) for patients taking basal insulin 30 to 60 units/d.55 The dose of IGlarLixi is administered once daily prior to the first meal of the day and should be titrated up or down by 2 to 4 units between 15 and 60 units every week.

IDegLira is initiated at a dose of 16 units (16 units degludec and 0.58 mg liraglutide).56 The dose of IDegLira is administered at the same time each day and should be titrated up or down by 2 units between 10 and 50 units every 3 to 4 days.

The pen devices for IGlarLixi and IDegLira are similar to the pen devices for their respective insulin products, which should simplify transitioning patients from the insulin product to the fixed-ratio combination product.

**CLINICAL IMPLICATIONS OF FIXED-RATIO BASAL INSULIN/GLP-1RAS**
The fixed-ratio basal insulin/GLP-1RA combination products combine 2 important patient-centered features: high levels of efficacy as represented by most patients achieving target treatment goals and superior glucose control compared with insulin. Furthermore, a single daily injection with no substantial dosing preparation should seem simple for patients. However, the use of these agents as the first injectable treatment may be limited by insurance coverage and cost, likely because this use is outside the currently approved indication. If these agents are added after basal insulin or GLP-1 RA, the provider should be mindful of the starting dose and discuss the expected glucose changes and common adverse reactions during titration.

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29. Holst JJ, Buse JB, Rodbard HW, et al. LixiLan improves fasting glucose as demonstrated using continuous glucose monitoring and a standard-

How often have you treated a patient with a medication for type 2 diabetes mellitus (T2DM) and found that the patient didn’t achieve the benefits you expected based on the results of a phase 3 randomized controlled clinical trial (RCT)? Perhaps your patient had a 0.6% reduction in glycated hemoglobin ($\text{HbA}_1\text{c}$) instead of 1% as reported in the RCT. Or maybe you found that hypoglycemia occurs in 20% of your patients treated with a specific medication per month rather than the 3% reported in the latest RCT of that medication. Such differences between RCTs and real life are common.

A recent analysis of an observational cohort of 917,440 adults with diabetes in the Surveillance, Prevention, and Management of Diabetes Mellitus network showed that the rate of severe hypoglycemia ranged from 1.4 to 1.6 events per 100 person-years.\(^1\) In contrast, a systematic review of 216 RCTs in patients with T2DM by Bolen et al found that few RCTs reported even 1 case of severe hypoglycemia for most classes of medications (except sulfonylureas or insulin for which hypoglycemia is very common) as mono-, dual, or triple therapy.\(^2\)

Why are there differences between the results observed in RCTs and those achieved in real-world clinical practice? Do these different data sets serve different purposes? If so, what? What are the benefits and limitations of each? Before we begin answering these questions, it is important to become familiar with key terminology (\textbf{TABLE 1}).\(^3\) The primary source for these definitions is the US Food and Drug Administration’s (FDA) 2017 \textit{Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices}; universal acceptance is not implied. Nonetheless, the definitions provided here can be used for a general understanding. Two particularly important terms are real-world data (RWD) and real-world evidence (RWE). RWD are data collected from a variety of sources outside of an RCT that relate to patient health status and/or delivery of health care. RWE is clinical evidence regarding the usage and potential benefits and/or risks of a medical product derived from analysis of RWD.\(^4\)\(^5\)

\textbf{RANDOMIZED CLINICAL TRIALS}

Traditional RCTs are the “gold standard” for clinical research because they enable a direct comparison of the impact of ≥2 interventions on ≥1 outcomes, often efficacy and safety. To do this, an RCT is designed to minimize the impact of external factors on outcomes by strictly controlling the study methods, ie, setting, characteristics of the patient population, interventions, the primary and secondary outcomes, as well as the statistical analyses. Typical—but not universal—
features of RCTs involving medications are:
- prospective design
- randomization of study participants between/among treatment arms
- strict inclusion and exclusion criteria
- specific use and dose(s) of interventions
- extensive, regimented monitoring that often involves more frequent patient visits than would occur in usual clinical practice
- extensive patient support and education

RCTs or safety/efficacy trials often compare the interventions of interest, such as an investigational medication or biologic, with placebo or sometimes with an established drug to determine whether the medication produces the expected result under ideal conditions. Although valuable for research and required for regulatory purposes, such a comparison might not be entirely helpful to a clinician who often is more

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Glossary of terms³-⁵</th>
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</thead>
<tbody>
<tr>
<td><strong>Term</strong></td>
<td><strong>Definition</strong></td>
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<tr>
<td>Average treatment effect</td>
<td>The average effect of treatment on those participants who received the treatment⁵</td>
</tr>
<tr>
<td>Effectiveness trial</td>
<td>Also called a pragmatic trial, measures the degree of beneficial effect under real-world clinical settings⁴</td>
</tr>
<tr>
<td>Efficacy trial</td>
<td>Also called an explanatory trial, determines whether an intervention produces the expected result under ideal circumstances. Most randomized controlled trials are efficacy trials</td>
</tr>
<tr>
<td>Medical administrative claims data</td>
<td>Claims arising from a person's use of the health care system (and reimbursement of health care professionals for that care)</td>
</tr>
<tr>
<td>Observational study</td>
<td>A study that does not involve any interventions (experimental or otherwise) on the part of the investigator, eg, a population study in which changes in health status are studied in relation to changes in other characteristics. Most analytical epidemiologic designs (notably, case-control and cohort studies) are called observational because investigators observe without intervening other than to record, classify, count, and analyze results</td>
</tr>
<tr>
<td>Post-marketing surveillance</td>
<td>Collection, analysis, and interpretation of data or other information about a marketed device or drug</td>
</tr>
<tr>
<td>Propensity score</td>
<td>The probability of treatment assignment conditional on observed baseline characteristics. It allows one to design and analyze an observational (nonrandomized) study so that it mimics some of the particular characteristics of a randomized controlled trial. This is achieved by balancing the distribution of observed covariates between treated and untreated subjects so that they are similar at baseline⁶</td>
</tr>
<tr>
<td>Propensity score matching</td>
<td>The formation of matched sets of treated and untreated subjects who share a similar value of the propensity score. This enables the estimation of the average treatment effect for the treated. The most common is 1-to-1 pair matching, in which pairs of treated and untreated subjects are formed, such that matched subjects have similar values of the propensity score⁵</td>
</tr>
<tr>
<td>Prospective study</td>
<td>Also called a concurrent cohort study, defines the original population of interest at the start of the study and collects exposure/treatment and outcome data from that time point forward. The start of the study is defined as the time the research protocol for the specific study question was initiated</td>
</tr>
<tr>
<td>Randomized or traditional clinical trial</td>
<td>Typically conducted in specialized research settings with a specific population. These studies often utilize measures designed to control variability and ensure data quality, such as detailed eligibility criteria, detailed case report forms that exist apart from medical records, and intensive monitoring and auditing designed to ensure precise adherence to study procedures and rigorous precision in data collection. They typically also include substantial efforts to ensure compliance with treatments and to avoid concomitant treatments that might influence the randomized treatment effect</td>
</tr>
<tr>
<td>Real-world data</td>
<td>Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (outside of a randomized controlled trial)</td>
</tr>
<tr>
<td>Real-world evidence</td>
<td>Clinical evidence regarding the usage and potential benefits and/or risks of a medical product derived from analysis of real-world data</td>
</tr>
<tr>
<td>Registry</td>
<td>An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves ≥1 predetermined scientific, clinical, or policy purposes</td>
</tr>
<tr>
<td>Retrospective analysis</td>
<td>Also called an historical cohort study, defines the population and determines the exposure/treatment from historical data. The variables and outcomes of interest are determined at the time the study is initiated</td>
</tr>
</tbody>
</table>
interested in the effectiveness and safety in patients who are more similar to those he or she sees and relative to best current or most common practice.6

Therefore, RCTs assess the efficacy and safety of the medication, whereas real-world studies evaluate the effectiveness of the medication, including the degree of beneficial effect under real clinical practice conditions.1 Differences between efficacy and effectiveness might be larger for medications that produce benefits over many years such as for a chronic disease, but smaller for an acute disease where benefits are observed more quickly.7 Differences between efficacy and effectiveness also might be larger for medications used in a diverse population because of the wide heterogeneity of patient characteristics that might impact outcomes.7

As noted above, a key characteristic of an RCT is the use of strict inclusion and exclusion criteria. This creates a well-defined patient population that generally is younger and healthier and whose sociodemographic characteristics are more homogeneous than patients treated with the medication in the real world.3,6,8 Furthermore, non-white races, women, and older adults often are underrepresented in RCTs, while pregnant women and children often are excluded in pre-approval clinical trials. Previous and concomitant treatment often is limited. Consequently, the narrowly defined population in an RCT could represent only a small percentage of patients expected to be treated with the medication in the real world. Thus, the internal validity attained in RCTs often limits the generalizability or relevance of the RCT results to other patient populations.9 Because of the highly selected population, careful clinical management, and relatively short trial period, patients in RCTs might be less likely to experience adverse events and clinical outcomes than real-world populations, which may lead to an underestimation of a medication’s adverse outcomes in clinical practice.4

Another limitation of RCTs is that patients who elect to participate in RCTs often are highly motivated, although motivating factors can vary significantly by condition.10-13 High rates of treatment adherence generally are observed in RCTs because of extensive patient support and education with frequent patient visits. For example, retrospective analysis of the Optum/Humedica claims database showed that only 29% and 37% of patients treated with a glucagon-like peptide-1 receptor agonist or dipeptidyl peptidase-4 inhibitor, respectively, were adherent over 1 year.14 By comparison, investigators estimated the adherence rate to be 95% in RCTs of these agents.14

Historically, RCTs have not assessed health care resource utilization or direct and indirect costs because the types of primary clinical endpoints used are less likely to correspond with the optimal endpoint for economic evaluation, such as quality-adjusted life years, hospitalization or office visit costs, medication costs, and missed work time.6 Moreover, the use of a composite of several endpoints as is sometimes done in an RCT, generally does not lend itself to cost per composite clinical endpoint. In contrast, clinical endpoints that focus on the treatment’s impact on how a patient feels, functions, or survives are useful for economic evaluation.6,15

SHIFTING FOCUS
Increasing recognition of the limitations of RCTs, particularly their limited generalizability to real-world clinical practice, has been paralleled by decades of concerns about escalating health care costs with only modest improvements in health care quality.9 The shift from volume-based to value-based payment has stimulated further interest in estimating how a medication or intervention affects care quality and spending in the real world. It also has stimulated interest in treatment decision-making for and by an individual patient.

Making these value-based estimates is not new; they have been done for decades using population health data, usually on a national or regional level through the use of insurance claims databases or registries.16 On a local level, hospitals and clinicians have used patient level data for quality and safety monitoring via chart audit.

Now the availability of patient-level data in electronic health records that includes data across the health care system has not only streamlined the collection and analysis processes, it often provides a more complete picture of the patient experience. When it doesn’t, claims databases can be used to provide missing data elements. There has been expansion in the size and types of databases available; therefore, the term “big data” often is used when referring to some RWD sources.17 Databases commonly used for real-world studies of patients with diabetes include Truven Health Analytics MarketScan, Optum Humedica SmartFile, GE Healthcare Centricity Practice Solution, IBM Explorys, and Kaiser Permanente. In some countries, health data of nearly the entire population is available for analysis from resources such as the United Kingdom Clinical Practice Research Datalink.

REAL-WORLD EVIDENCE
The role of RWE in health care decision making, as well as regulatory affairs and drug development, is expanding. Current and evolving uses of RWE include changes in product labeling by the FDA, the development of a personalized treatment plan by patients and physicians, use as a tool for quality improvement, and measurement of health care resource utilization and associated costs.17 RWE also can be used to provide information about clinical questions when RCTs would be impractical to conduct because they might require
There is no universally accepted definition of RWD. In its broadest terms, RWD refers to data obtained outside of an RCT. RWD can be gathered retrospectively, as commonly used for health outcomes research, or prospectively, as may be used for safety monitoring or a pragmatic trial. As with RCTs, data quality is of paramount importance. The RWD used to develop RWE must be high-quality. Because RWD often are taken from multiple but heterogeneous sources, it is important that RWD is refined before analysis and interpretation as RWE. For example, a HbA1c level might be documented using a procedure code as well as in a clinician note. Steps must be taken to ensure the data are consistent. Another example is where information is absent in 1 data source, eg, electronic health record, and might need to be filled from another source, eg, claims database.

The length of an RWE trial sometimes is longer than an RCT so that accurate assessment of health outcomes can be made. RWE trials generally involve a simple design and include a large sample size, often tens of thousands patients, from diverse settings. Application of exclusion criteria and techniques such as propensity score matching (see TABLE 1) could reduce the number of patients. Large datasets allow the use of novel data analytics such as machine learning and predictive modelling.

In RWE trials, standard treatment or current practice is a typical comparator, although new treatments could be used. Consequently, similar to RCTs, RWE trials of medications could include patient populations or indications not approved by the FDA. In contrast to RCTs, RWE trials allow patients and their clinicians to choose treatments based on clinician preference, as well as the patient’s characteristics and preferences.

There are many potential limitations to RWE trials. Most RWE trials involve nonrandomized patients where it often is not known why patients were assigned to a particular treatment or intervention, which can introduce confounding. To correct for nonrandomization, patient groups might be matched using covariate adjustment, propensity scores, etc; nonetheless, selection bias and other confounders could remain. Patient accrual over a reasonable period of time might be difficult, particularly for a medication with low usage or rare condition. Data may be of poor or unknown quality or missing leading to random or systematic bias. The collection and analysis of RWD can be costly.

Limitations among RWD sources are common as well. For example, electronic medical record data and patient registries could consist of variable types and quality of information. Some data elements might be missing from these sources as well as from claims data and there may be limited follow up of some patients. Moreover, the reasons patients initiate or change treatments often are not available. These limitations should not exclude the use of these sources, but should be documented so that their impact on analysis and interpretation can be understood.

The challenges presented with the limitations of RWD are a focus of active efforts by the FDA, National Institutes of Health, pharmaceutical manufacturers, and other stakeholders.

# CASE EXAMPLES

**Beta-blocker therapy post-myocardial infarction**

An early example of how RWD can lead to practice change...
involves the use of beta-blockers in patients who had experienced a myocardial infarction (MI). In the 1990s, Medicare sponsored the Cooperative Cardiovascular Project, which analyzed medical records of >200,000 people who had experienced an MI. The analysis showed that patients who had vs those who had not received a beta-blocker following an MI, including those with a contraindication to beta-blocker therapy, experienced a substantial reduction in mortality (relative risk, 0.67; 95% CI, 0.62 to 0.72). These results supported similar evidence from some earlier clinical trials, helping to make beta-blocker therapy standard care in patients with an MI.

Insulin glargine 300 units/mL

Differentiate Gla-300 clinical and Economic in real-world Via EMR Data study (DELIVER 2) was a retrospective analysis of the Predictive Health Intelligence Environmental database. The purpose of the analysis was to evaluate clinical outcomes of patients with T2DM currently using basal insulin who were then switched to either insulin glargine, 300 units/mL, or other basal insulins in real-world practice. (The reason for the switch is not included in the dataset.) Patients who switched to insulin glargine, 300 units/mL, (N = 2196) or other basal insulins (N = 3837) were compared following 1:1 ratio propensity score matching (N = 1819 in each cohort). From a baseline of 8.95% and 8.93%, HbA1c reductions were comparable in both cohorts (−0.51% vs −0.51%, respectively; P = .928). At 6 months, fewer patients who switched to insulin glargine, 300 units/mL, experienced hypoglycemia compared with those who switched to other basal insulins (15.4% vs 18.1%, respectively; P = .015). After adjusting for baseline hypoglycemia, switching to insulin glargine, 300 units/mL, was associated with a significantly lower rate of hypoglycemia compared with switching to other basal insulins (difference between least squares means of 0.15 events/patient-year; P = .041 favoring insulin glargine, 300 units/mL). Incidence and event rates of hypoglycemia requiring hospitalization or emergency care also were significantly lower with insulin glargine, 300 units/mL, contributing to an overall savings of $1439 per patient per year. In a real-world setting, switching to insulin

**FIGURE** Hypoglycemia event rates in randomized controlled trials vs real-world data studies

- a. Nonsevere/confirmed
- b. Severe
- c. Nocturnal

Abbreviations: RCT, randomized controlled trial; RWD, real-world data; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

The number of studies in each subgroup is shown in parentheses.

glargine, 300 units/mL, was associated with a significantly lower risk of hypoglycemia, including hypoglycemia associated with hospitalization or emergency department visit, than switching to other basal insulins, while delivering comparable glycemic control.

**Hypoglycemia in insulin-treated diabetes**

The frequency of hypoglycemia in patients with type 1 diabetes mellitus (T1DM) or T2DM has been compared in real-world settings vs RCTs. A structured literature review of studies from 2010 to 2014 identified 6 involving patients with T1DM (4 RCTs, 2 RWDs) and 25 involving patients with T2DM (15 RCTs, 10 RWDs). The minimum study duration was 26 weeks for RCTs; there was no minimum for RWD studies. A minimum of 400 patients were required in each study. Case study reports and database studies were excluded from the RWD studies, the latter because the investigators felt they do not provide an accurate representation of overall hypoglycemia.

Higher rates of hypoglycemia generally were observed in RWD studies vs RCTs in patients with T1DM or patients with T2DM treated with basal-bolus or basal-oral therapy, although there was some overlap in the range of reported event rates (FIGURE, see previous page). These findings indicate that the true burden of hypoglycemia might be underestimated in RCTs, probably resulting from carefully selected patients, carefully titrated dosing using a treat-to-target approach, closer supervision and blood glucose monitoring, and typically shorter duration. In interpreting these results, one must keep in mind that RWD studies also might underestimate the true burden of hypoglycemia because blood glucose monitoring from self-monitoring or continuous glucose monitoring might not be available or collected as frequently as occurs in RCTs.

**IMPLICATIONS OF REAL-WORLD DATA**

RWE based on RWD is gaining importance as a complement to randomized controlled trials. The primary attribute that distinguishes RWE from other kinds of evidence is the clinical care and community settings as opposed to research-intensive or academic environments. The premise is that real-world data can be collected from multiple sources that include extremely large samples of patients in real-world clinical practice, then appropriately analyzed and evaluated to yield RWE that can be generalized to a broader population of patients treated with the medications, devices, or other interventions. This may include patient subgroups often excluded in RCTs, eg, older patients, children, those with renal impairment, etc. Therefore, RWE likely could facilitate improved management of patients. Barriers and limitations to RWE studies exist, however. But as these are increasingly addressed, RWE likely will have wider application in clinical research, regulatory review and approval, postapproval outcomes, and post-marketing surveillance.

**REFERENCES**


INTRODUCTION
Colorectal cancer (CRC) is the fourth most common cancer diagnosed in the United States and, despite its potential for early detection, remains the second most common cause of oncology-related deaths for US men and women combined. An estimated 140,250 patients will be newly diagnosed in 2018, and 50,630 CRC-related deaths will occur. The incidence of and mortality related to CRC are greater in men than women, and CRC affects more non-Hispanic blacks than non-Hispanic whites (males: 56.4 vs 45.2 per 100,000, respectively; females: 41.7 vs 34.5 per 100,000, respectively). Risk for CRC increases with age, as adults aged 65 to 74 years are most commonly diagnosed. Moreover, risk increases in individuals with a family history of CRC (1.9-fold) or inflammatory bowel disease (2.9-fold). Regardless of risk, screening has improved early detection rates and reduced CRC-related mortality. Additionally, screening can detect adenomatous polyps and villous adenomas, with malignancy rates of 34.5% for patients with severe atypia, and 48.0% for those with severe atypia and polyp size >2 cm. Discovery of adenomatous polyps and villous adenomas is key for detecting early-stage CRC, when the potential to treat and cure the disease is greatest. Five-year survival rates are high with localized disease (stage I, 93.9%), but decrease as CRC spreads to lymph nodes and metastasizes (stage IV, 11.4%; FIGURE 1). Consequently, encouraging screening for early detection of polyps and localized cancers is an important role for primary care providers.

COLORECTAL CANCER SCREENING
The importance of screening to detect and diagnose early-stage CRC, as well as the favorable effect of screening on CRC-related mortality, has been established. In the United States, CRC-related mortality decreased 51%, from 28.6 to 14.1 per 100,000, from 1976 to 2014, in part related to a 14% decrease attributed to screening. In one study (N=9437 diagnoses), screening resulted in the diagnosis of a significantly greater percentage of early-stage CRC diagnoses (stages I and II) than late-stage CRC (stages III and IV; 66.7% vs 39.8%, respectively; P<.001). A second study (N=1129 patients) reported similar findings, with a significantly greater percentage of CRCs detected in the early stage due to screening versus symptom-based detection (67% vs 45%, respectively; P<.001). Screening colonoscopy and guaiac-based fecal occult blood testing (gFOBT) significantly decreased the risk of CRC-related mortality versus symptom-based detection (colonoscopy: hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.21-0.60; gFOBT: HR, 0.47; 95% CI, 0.29-0.77). A 15% reduction in the US incidence of CRC from 2007 to 2020 could save lives (~150,000 life-years saved) and result in a lifetime health care cost savings of approximately $624 million (2013 dollars). Further, achieving a screening rate of 80% by 2018 in adults aged ≥50 years in the United States is projected to result in an estimated 43,000 fewer cases per year by 2030, with a mortality decrease by 203,000 total deaths from 2013 to 2030.

For asymptomatic adults aged 50 to 75 years at average risk for CRC, the US Preventive Services Task Force (USPSTF) and American Cancer Society (ACS) clinical practice guidelines recommend routine screening using one of a number
CRC screening for patients aged 50 to 75 years to be an “A” rated process and emphasized choice through shared decision-making, with the goal of increasing the number of individuals who undergo CRC screening. Routine screening is appropriate for adults considered healthy enough to undergo treatment if CRC is detected and without comorbidities limiting life expectancy. The risk of developing CRC is increased in individuals with a personal or family history of CRC or polyps, a personal history of ulcerative colitis or Crohn’s disease, or a family history of a hereditary CRC syndrome (eg, familial adenomatous polyposis). With that in mind, these individuals may need to initiate screening before age 50 years and/or may require more frequent screening, depending on the specific risk-related factor(s).

As noted in clinical practice guidelines, several stool-based (noninvasive) and direct visualization methods can be used to accurately detect polyps and early-stage CRC during routine screening (TABLE 1). Given detection considerations (eg, polyps and early-stage cancer may only bleed intermittently), guidelines recommend stool-based testing be performed at more frequent intervals than direct visualization methods. A positive result with any stool-based test requires follow-up diagnostic colonoscopy. The harms associated with stool-based testing are minimal and primarily result from adverse events related to the diagnostic colonoscopy procedure following a positive stool-based test. Annual screening using gFOBT, which detects the presence of the heme portion of human hemoglobin in stool, is convenient because 3 stool samples can be collected at home without bowel preparation prior to sample collection. However, dietary and medication restrictions are associated with gFOBT. gFOBT was shown to be associated with a 32% decrease in CRC-related mortality compared with no screening (relative risk [RR], 0.68; 95% CI, 0.56-0.82). The sensitivity of gFOBT for the detection of serrated (premalignant) polyps or advanced CRC was low (2.6% and 7.4%, respectively; TABLE 2), while specificity was high (98.4% and 98.6%). In one study (N=997 patients), the percentage of patients adherent to CRC screening with annual gFOBT (n=344) over a 3-year period decreased over time, from 67% in year 1 to 27% and 14% in years 2 and 3, respectively. Similarly, 46.6% of individuals in

![FIGURE 1 Colorectal cancer stages and 5-year survival rates](image)

![FIGURE 2 Summary of ACS and USPSTF guideline recommendations for CRC screening for individuals between ages 50 and 75 years at average risk of developing CRC](image)

**Abbreviations:** ACS, American Cancer Society; CRC, colorectal cancer; CT, computed tomography; FIT, fecal immunochemical test; FIT-DNA, fecal immunochemical test-multi-target stool DNA test; gFOBT, guaiac fecal occult blood test; mt-sDNA, multi-target stool DNA; USPSTF, US Preventive Services Task Force.

*Guideline recommendations differ between ACS and USPSTF.
†Screening option according to USPSTF, but not ACS.
Adapted from American Cancer Society CRC screening guidelines and Bibbins-Domingo et al.
TABLE 1  Characteristics of CRC screening methods

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stool-based (noninvasive) tests</th>
<th>Direct visualization tests</th>
<th>Flexible sigmoidoscopy</th>
<th>Flexible sigmoidoscopy with FIT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>gFOBT</td>
<td>FIT</td>
<td>mt-sDNA test</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td></td>
<td>In-home testing</td>
<td>In-home testing</td>
<td>In-home testing</td>
<td>Entire colon examined by imaging</td>
</tr>
<tr>
<td></td>
<td>No bowel preparation or sedation required</td>
<td>No bowel preparation or sedation required</td>
<td>No bowel preparation or sedation required</td>
<td>Less invasive vs colonoscopy</td>
</tr>
<tr>
<td></td>
<td>Single stool sample collection</td>
<td>Single stool sample collection</td>
<td>No dietary or medication restrictions</td>
<td>Less frequent screening requirement</td>
</tr>
<tr>
<td></td>
<td>No dietary or medication restrictions</td>
<td>Screens for altered DNA biomarkers in stool</td>
<td>Biopsy or polyp removal during same procedure</td>
<td>Less volumes of bowel preparation vs colonoscopy</td>
</tr>
<tr>
<td></td>
<td>Greatest benefits to harms ratio (vs other modalities)</td>
<td>Embedded patient compliance program</td>
<td>Detection of extracolonic abnormalities</td>
<td>Less sedation required</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Lower sensitivity than mt-sDNA</td>
<td>Lower sensitivity than mt-sDNA</td>
<td>Lower specificity than FIT</td>
<td>Bowel preparation and sedation required</td>
</tr>
<tr>
<td></td>
<td>Serial stool sample collection</td>
<td>Positive findings require diagnostic colonoscopy</td>
<td>Bowel preparation and sedation required</td>
<td>Potential adverse effects related to bowel preparation, sedation, or procedure</td>
</tr>
<tr>
<td></td>
<td>Potential inability to detect carcinomas with little to no bleeding</td>
<td>Potential inability to detect carcinomas with little to no bleeding</td>
<td>Physician skill dependent</td>
<td>Physician skill dependent</td>
</tr>
<tr>
<td></td>
<td>Requires dietary and possible drug administration restrictions prior to testing</td>
<td>Requires dietary and possible drug administration restrictions prior to testing</td>
<td>Patient time requirement (bowel preparation and test)</td>
<td>Patient time requirement (bowel preparation and test)</td>
</tr>
<tr>
<td></td>
<td>Lower specificity than FIT</td>
<td>Positive findings require diagnostic colonoscopy</td>
<td>Test performed at health care facility</td>
<td>Test performed at health care facility</td>
</tr>
<tr>
<td></td>
<td>Positive findings require diagnostic colonoscopy</td>
<td>—</td>
<td>Patient requires transportation home after procedure</td>
<td>Positive findings require diagnostic colonoscopy</td>
</tr>
<tr>
<td><strong>Adherence or compliance with screening†</strong></td>
<td>Adherence FIT vs gFOBT: RR, 1.2 (95% CI: 1.03-1.3)</td>
<td>Compliance 88.3%</td>
<td>Adherence colonoscopy vs gFOBT/FIT: RR, 0.6 (95% CI: 0.4-0.8)</td>
<td>Adherence flexible sigmoidoscopy plus gFOBT/FIT vs gFOBT/FIT: RR, 0.6 (95% CI: 0.4-0.9)</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>Adherence endoscopy vs stool-based tests: RR, 0.7 (95% CI: 0.6-0.8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>Adherence flexible sigmoidoscopy vs stool-based tests: RR, 0.8 (95% CI: 0.6-1.04)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CRC, colorectal cancer; CT, computed tomography; FIT, fecal immunochemical test; gFOBT, guaiac-based fecal occult blood test; mt-sDNA, multi-target stool DNA; RR, relative risk.

*Defined as colonic distension with air or carbon dioxide.
†Data presented limited to meta-analysis or study of single screening modality (mt-sDNA).
a multicenter health care system returned for annual gFOBT testing, while 35.3% were inconsistent with annual screening and 18.1% did not return for repeat screening.30

Annual fecal immunochemical testing (FIT), which utilizes antibodies to detect the presence of the globin portion of human hemoglobin in stool, may have comparable sensitivity with, but improved specificity for, detection of CRC compared with gFOBT.32 The pooled one-time sensitivity of FIT, determined from a single meta-analysis of FIT studies using colonoscopy as the reference standard, is 71%, with a specificity of 94%.41 In another study, FIT sensitivity for all stages of CRC was 74%, which decreased to 73% for stages I-III CRC, 46% for high-grade dysplasia, 24% for advanced adenomas measuring 1 cm or greater, and 5% for sessile serrated (flat, premalignant) polyps.21 Unlike gFOBT, FIT typically requires a single stool sample collected at home, without dietary or medication restrictions prior to sample collection; as with gFOBT, no bowel preparation is needed.3,30,34,42 In one study, FIT (n=4662) detected a significantly greater percentage of advanced neoplasias (ie, CRC or advanced adenoma) compared with gFOBT (n=3236; 0.8% vs 0.3%, respectively; P=.003).43 Meta-analysis of 5 randomized studies found FIT detected advanced neoplasia (ie, CRC, or polyp ≥10 mm or with high-grade dysplasia or villous component) and CRC with greater accuracy than gFOBT (advanced neoplasia: RR, 2.3; 95% CI, 1.7-3.1; CRC: RR, 2.0; 95% CI, 1.2-3.2) following adjustment for adherence to screening.27 A meta-analysis of 5 studies demonstrated adherence to FIT was greater than to gFOBT (RR, 1.2; 95% CI, 1.03-1.3).27 However, "real world" year-over-year adherence rates with FIT are often far less than 30%. In one study, only 0.3% of nearly 98,000 individuals were found to have completed 10 consecutive years of FIT testing.44 Over a 3-year period, individuals eligible for CRC screening who received annual FIT kits by mail had greater screening completion rates compared with people receiving a screening recommendation during an outpatient visit with their provider (28.0% vs 10.7%, respectively).45

In August 2014, the multi-target stool DNA (mt-sDNA) test, which analyzes 11 distinct molecular biomarkers from cells that shed into the intestinal tract to simultaneously detect epigenetic changes in DNA, specific DNA mutations, and human hemoglobin in stool, was introduced as a screening test for adults at average risk of developing CRC.21,46 mt-sDNA testing, which is performed at home, requires a single stool sample and no bowel preparation, has no dietary or medication restrictions, and has the greatest benefits-to-harms

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**TABLE 2** Sensitivity of CRC screening methods21,35-39

<table>
<thead>
<tr>
<th>Detection parameter</th>
<th>Stool-based (noninvasive) tests</th>
<th>Direct visualization tests</th>
<th>Flexible sigmoidoscopy</th>
<th>Flexible sigmoidoscopy with FIT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>gFOBT</td>
<td>FIT</td>
<td>mt-sDNA test</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>Any CRC</td>
<td>61.5%-79.4%*</td>
<td>73.8%†</td>
<td>92.3%†</td>
<td>93.1%-99.5%†</td>
</tr>
<tr>
<td></td>
<td>62.3%-83.3%‡</td>
<td></td>
<td></td>
<td>75.6%-92.4%†</td>
</tr>
<tr>
<td>Advanced CRC</td>
<td>7.4%</td>
<td>22.3%</td>
<td>—</td>
<td>16.3%</td>
</tr>
<tr>
<td>Advanced adenoma</td>
<td>—</td>
<td>23.8%†</td>
<td>42.4%†</td>
<td>—</td>
</tr>
<tr>
<td>Adenoma ≥6 mm</td>
<td>—</td>
<td>—</td>
<td>92.3%</td>
<td>88.7%</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>—</td>
<td>75%-93%§</td>
<td>73%-98%§</td>
</tr>
<tr>
<td>Adenoma ≥10 mm</td>
<td>17.7%-49.4%*</td>
<td>—</td>
<td>87.5%</td>
<td>93.8%</td>
</tr>
<tr>
<td></td>
<td>89%-98%§</td>
<td></td>
<td>67%-94%§</td>
<td>93.1%-95%*</td>
</tr>
<tr>
<td>Serrated (premalignant) polyps</td>
<td>2.6%</td>
<td>4.2%-5.2%†</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

---

Abbreviations: CRC, colorectal cancer; CT, computed tomography; FIT, fecal immunochemical test; gFOBT, guaiac-based fecal occult blood test; mt-sDNA, multi-target stool DNA.

*Sensitivity comparison of method on top row vs method in left column.

†P=.002 (CRC) and P=.001 (advanced adenoma: includes sessile serrated [premalignant] polyps ≥1 cm) for mt-sDNA vs FIT.

‡Sensitivity of InSure FIT and OC FIT-CHEK.

§Based on meta-analysis data from 7 studies (CT colonography) or 4 studies (colonoscopy).38

¶Compared with CT colonography or colonoscopy plus CT colonography.26

#Based on simulation models incorporating multiple screening intervals, different ages at initiation of screening, and different ages at last screening.39
procedure. In asymptomatic individuals at average risk for developing CRC, Imperiale et al.\(^\text{21}\) showed mt-sDNA testing had superior sensitivity for detecting CRC (any disease stage) and advanced adenomas versus FIT (CRC: 92.3% vs 73.8%, respectively, \(P<.002\); advanced adenomas: 42.4% vs 23.8%, \(P<.001\); TABLE 2).\(^\text{21,35-39}\) Results from Imperiale et al. demonstrated false-negative rates of 13% and 8.5% for patients aged 50 to 84 years, and 50 to 64 years, respectively.\(^\text{21}\) For patients previously noncompliant with other screening modalities (ie, >10 years since last colonoscopy and/or >1 year since last gFOBT; \(N=393\)), 88.3% completed screening by mt-sDNA testing within 1 year.\(^\text{28}\) An initial mt-sDNA rescreening interval of 3 years is included in nationally recognized guidelines from ACS\(^\text{20}\); USPSTF guidelines recommend an interval of either 1 or 3 years.\(^\text{3}\) The Centers for Medicare and Medicaid Services has approved mt-sDNA reimbursement for a rescreening interval of 3 years.

Direct visualization screening methods include colonoscopy, computed tomography colonography (CTC), and flexible sigmoidoscopy with or without annual FIT. Direct visualization CRC screening modalities are considered more invasive than stool-based tests, typically require bowel preparation, medication and/or dietary changes, anesthesia and subsequent need for transportation following the procedure, time away from work and other responsibilities, and are performed at an outpatient health care facility or hospital.\(^\text{1}\) Colonoscopy allows for the visualization of the entire colon and rectum through a colonoscope.\(^\text{3,9}\) CTC, also referred to as virtual or CT colonoscopy, allows for detailed imaging of the entire colon and rectum by inflating the colon with air or carbon dioxide and running the patient through a CT scanner.\(^\text{9,47}\) Colonoscopy examination, the patient will need to follow up with a colonoscopic polypectomy to have the lesion removed.\(^\text{3,56}\)

Meta-analysis of asymptomatic or screening populations showed patients undergoing colonoscopy are at low risk for perforations (\(n=26\) studies; 4 in 10,000 procedures) or major bleeding (\(n=22\) studies; 8 in 10,000 procedures); 36% of perforations and 96% of cases of major bleeding occurred during polyp removal (\(n=8\) studies).\(^\text{38}\) Similarly, meta-analysis of 11 studies showed the rate of perforation in asymptomatic individuals was low (0.02%; \(n=6\) studies) with CTC; the rate of perforation due to insufflation was 0.03% (\(n=7\) studies).\(^\text{51}\)

Flexible sigmoidoscopy is not commonly used as a CRC screening test in the United States.\(^\text{54}\) Flexible sigmoidoscopy involves endoscopic examination of the distal colon following cleansing by enema\(^\text{49}\) and may not detect polyps and CRC localized to the proximal colon. The limitations of flexible sigmoidoscopy were confirmed in an analysis of US cancer registry data showing CRC occurred more often in the right side (proximal) than the left (distal) side of the colon (43.5% vs 37.7%, respectively).\(^\text{55}\) The overall CRC sensitivity of flexible sigmoidoscopy is limited, but is generally assumed to be comparable to that of colonoscopy for distal colon examination. In one study, 17% of undetected lesions were beyond the reach of flexible sigmoidoscopy.\(^\text{56}\) If the medical professional finds a lesion greater than 1 cm during flexible sigmoidoscopy examination, the patient will need to follow up with a colonoscopic polypectomy to have the lesion removed.\(^\text{56}\) Current USPSTF and ACS guidelines recommend screening of asymptomatic individuals in the United States every 5 years when using flexible sigmoidoscopy.\(^\text{1,20}\) Flexible sigmoidoscopy every 10 years, combined with annual FIT, is recommended in USPSTF guidelines (FIGURE 2) and demonstrated increased sensitivity for detecting advanced neoplasia or any CRC compared with either screening method alone (TABLE 2).\(^\text{21,35-39,57}\)
The digital rectal exam is not recommended for CRC screening, as testing is limited to the lower rectum. Further, any stool found during a digital rectal exam should not be screened for CRC by gFOBT or FIT. Recently, the Septin 9 serum assay was approved by the US Food and Drug Administration for the screening of adults aged ≥50 years who have been offered, but not completed, CRC screening. However, current ACS and USPSTF guidelines do not include mention of the Septin serum assay.

**POTENTIAL BARRIERS TO CRC SCREENING**

Potential barriers to CRC screening include issues relevant to patients and providers (FIGURE 3). Prior to implementation of the Affordable Care Act (ACA) in 2010, individuals with coverage through private insurers or Medicare were responsible for a portion of screening-related costs, a potential impediment to CRC screening. The ACA provides individuals access to preventive care, including CRC screening, with no out-of-pocket costs. It is unclear if the need for a follow-up diagnostic colonoscopy following a positive stool-based screening test, which may be associated with out-of-pocket costs, is a barrier to CRC screening.

Surprisingly, after ACA implementation, the elimination of cost sharing did not increase the uptake of CRC screening among individuals with private insurance or Medicare (2009 to 2011/2012). Similarly, analysis of a sample of Medicare beneficiaries showed colonoscopy use for CRC screening was unchanged or decreased following ACA implementation compared with the prior 2 years. However, National Health Interview Survey data showed a significant increase in the percentage of adults aged 50 to 75 years undergoing CRC screening from 2008 to 2013 (57.3% to 61.2%; P<.001). Notable increases in CRC screening occurred in individuals classified as low-income (<$35,000 annual household income; 4.3% increase; P=.02) and middle-income ($35,000 to <$75,000 annual household income; 3.5% increase; P=.04), and in adults with Medicare coverage (9.8% increase; P<.001) and Medicare plus private insurance (5.9% increase; P=.002); 61.8% of adults included in the dataset were covered by private insurance. Thus, elimination of patient economic barriers is one factor of importance for increasing CRC screening in some individuals.

For some patients, the invasive nature of a colonoscopy presents a significant barrier. Data suggest there are 2 distinct groups: individuals who prefer colonoscopy and individuals who prefer noninvasive (stool-based) testing. Another potential barrier is the role of patient perceptions, as 80.6% of 175 providers surveyed “sometimes” or “usually” encountered individuals unaware of the seriousness of CRC. Additional barriers for individuals eligible for CRC screening include issues regarding privacy, inconvenience of testing, concerns with accuracy of testing, frequency of screening required, bowel preparation requirements, invasiveness of testing, and availability of patient support services.

Primary care providers play an important role in preventive screening. In one study, individuals with ≥1 primary care visit in 1 year were more likely to have completed CRC screening compared with patients with no annual provider contact (63.1% vs 42.2%, respectively; odds ratio [OR], 2.3; 95% CI, 2.3-2.4). The substantial demand on a provider’s time may also play a role in the stagnant rates of CRC screening in the United States; providers would have to work an estimated 21.7 hours per day to address all acute and chronic disease and preventive care guideline recommendations. Provider time constraints are anticipated to increase as a result of expanded health care access through the ACA; thus, the role of nurse practitioners and physician assistants in preventive care, including CRC screening, is likely to expand.

Shared decision-making regarding CRC screening methods is an important factor in adherence. In a 2016 longitudinal study of more than 150,000 eligible adults older than 50 years of age, one-third failed to adhere to current USPSTF CRC screening recommendations over a 10-year period, whether they underwent colonoscopy, flexible sigmoidoscopy, FIT, or gFOBT. However, in one study, individuals 50 to 79 years of age at average risk of developing CRC were significantly more likely to adhere to screening when permitted to choose the method (eg, colonoscopy, gFOBT) compared with individuals recommended colonoscopy only (68.8% vs 38.2%, respectively; P<.001). Barriers primary care providers may encounter in shared decision making include language and technological limitations, as some patients lack internet access or the skills required to navigate internet-based educational tools.

Increasing screening rates with stool-based testing may require increased patient navigation. In a study of eligible...
individuals randomly assigned to receive usual care (ie, screening method recommended during outpatient visit; n=1199), reminder mailings for colonoscopy (n=2400), or FIT kits sent by mail annually (n=2400), outreach led to greater screening completion rates versus usual care over a 3-year period (colonoscopy, 38.4% and annual FIT, 28.0%, vs usual care, 10.7%).45 However, a greater percentage of individuals in the colonoscopy group never initiated screening compared with the FIT group (44.0% vs 30.2%, respectively).45 These findings are consistent with data from another study, in which only 25.5% of 2010 individuals receiving FIT kits in the mail completed testing; patients were 50% more likely to complete FIT testing when reminded by a live phone call compared with a mailed letter.78

However, while adherence rates for stool-based CRC screening may be low in some studies,30,40 results of a meta-analysis indicated direct visualization screening tests had significantly lower adherence rates than stool-based testing (RR, 0.67; 95% CI, 0.56-0.80; TABLE 1).21-28 Thus, while USPSTF guidelines do not recommend one screening modality over another,3 stool-based (noninvasive) screening methods may be an option for patients who are nonadherent to direct visualization methods or indicate a preference for noninvasive testing modalities.

SUGGESTED PRACTICE IMPROVEMENTS FOR CRC SCREENING
Practice improvements to ensure CRC screening adherence for eligible individuals requires a team effort.79 Higher CRC screening rates have been associated with a number of practice improvement programs, such as engaging patients in shared decision-making and targeting interventions to specific groups.70,80 Indeed, practices with a commitment to CRC screening, including use of a script, have been shown to have significantly greater screening rates compared with practices less dedicated to providing CRC screening (57.2% vs 27.6%, respectively; P<.001).80

Common threads across successful programs include prioritizing CRC screening performance, redesigning the care delivery system, utilizing electronic medical record tools, involving all clinic staff, and engaging patients (FIGURE 4). Clinic staff should have defined roles, with accountability, in the process of improving CRC screening rates. Utilizing the medical assistant to review patients’ CRC screening status increased the monthly referral rate for colonoscopy by 85% (from 6.0% to 11.1%) at a regional network of 7 community clinics in 2005.81 At one community practice, CRC screening rates increased from 28% to 80% during a 2-year period, following reevaluation of testing used (eg, replacing gFOBT with FIT) and a redesign of the primary care team (eg, expanding the role of the medical assistant to include obtaining CRC screening status from patients, increasing outreach efforts).82 In a single Veteran’s Administration health care system (ie, multiple primary care clinics, hospital), replacing gFOBT with FIT resulted in a significantly greater percentage of patients completing testing (FIT, 42.6%; gFOBT, 33.4%; P<.001), which suggests that minor changes in processes, including changes
to more convenient methods of stool-based (noninvasive) testing, are effective in improving CRC screening rates.33

Patient care delivery system redesign may be needed to increase CRC screening rates, including determining individuals eligible for CRC screening prior to scheduled appointments, empowering clinic staff with standing orders, and establishing protocols for individuals who are nonadherent to CRC screening. For direct visualization screening, primary care clinic and specialty practice coordination may need to be implemented to ensure timely follow-up with individuals who miss testing or need assistance coordinating medications in advance of screening (eg, patients with diabetes).40 Further, close coordination between the primary care provider and specialist can help improve scheduling, bowel preparation, and adherence with follow-up procedures.41 While not yet documented in the literature, according to Curtis Gattis (Founder and CEO, LeadingReach, Austin, TX; written communication April 24, 2018, unreferenced), adoption of referral management software may improve accountability on both sides of the referral. By tracking and monitoring compliance, referral software can highlight at-risk patients not completing screening. Such simple but effective solutions help both primary care providers and large hospital systems to streamline referral relationships and processes, leading to better compliance and adherence to CRC screening guidelines.

Survey data indicate providers consider alerts in the electronic medical records database to be “somewhat” or “very” helpful interventions for support staff (93.7%; n=174 respondents) and providers (87.9%; n=174).73 Additionally, generating a daily list of individuals eligible for CRC screening has been helpful for increasing screening rates (77.7%; n=175).73 Periodic review of patients’ electronic medical records (eg, every 6 months) may be used to identify individuals eligible for CRC screening based on age or family history of CRC. Additionally, inclusion of all guideline-recommended screening modalities in the health maintenance template could increase CRC screening rates.

Finally, outreach efforts to engage patients in CRC screening by initiating contact through mail, phone, emails, or patient portals have the potential to increase CRC screening rates. Upon arrival at the clinic, patients could be greeted with educational information related to CRC screening methods. However, some individuals might appreciate further discussion with their provider regarding CRC screening.62 Reinforcing the importance of regular CRC screening with posters or written information is another suggestion for improving screening rates. At one health center, efforts to improve the convenience of CRC screening included mailing a FIT kit around the time of the patient’s birthday and providing at-home screening kits when individuals arrived for other clinic visits (eg, flu shots).20

The mt-sDNA test is currently the only USPSTF-recommended screening modality offering a patient compliance program and a multilingual (ie, 70 languages), US-based 24/7 customer support call center to address questions from patients and providers.29 The patient compliance program proactively establishes contact before the test is shipped to a patient’s home and continues communication via a series of phone calls and mailings to encourage completion of testing.29 Thus, improving uptake of CRC screening in primary care will involve participation across the entire health care continuum.

CONCLUSIONS

Colorectal cancer is a leading cause of cancer-related deaths in the United States, yet approximately one-third of individuals eligible for CRC screening remain unscreened according to recommended clinical practice guidelines. For individuals at average risk for developing CRC, guidelines recommend screenings begin at age 50 years. Providers and patients are encouraged to use shared decision-making to choose a patient’s preferred CRC screening option, ranging from noninvasive, convenient, at-home stool-based testing (eg, mt-sDNA, FIT, gFOBT) to more invasive, direct visualization methods (eg, colonoscopy, CTC), as screening by any modality is better than no screening at all. Practice improvements have been shown to increase uptake of CRC screening in clinical settings and may include replacing one method of screening with another or redesigning the patient care delivery system to increase CRC screening rates. Regardless of the screening modality used, there is a need to improve CRC screening rates in the general population by improving patient adherence to guideline recommendations and to continue to reduce CRC-related morbidity and mortality.61

REFERENCES


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