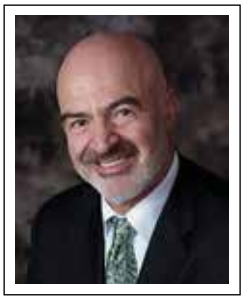
This supplement was sponsored by Primary Care Education Consortium and Primary Care Metabolic Group. The articles in this supplement were previously published in a supplement to The Journal of Family Practice. The articles were edited and peer reviewed by *The Journal of Family Practice*.

PRIMARY CARE EDUCATION CONSORTIUM
WWW.PCECONSORTIUM.ORG

PCMG Primary Care Metabolic Group
WWW.PCMG-US.ORG

SUPPLEMENT TO
Clinician Reviews®
VOL 28, NO 6 | AUGUST 2018 | WWW.MDEDGE.COM/CLINICIANREVIEWS

A SPECIAL SUPPLEMENT ON
Hot Topics in Primary Care



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

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

1. American Association of Nurse Practitioners. 2017 AANP National Nurse Practitioner Sample Survey.
2. National Commission on Certification of Physician Assistants. 2017 Statistical Profile of Certified Physician Assistants. http://prodcmsstoragesa.blob.core.windows.net/uploads/files/2017StatisticalProfileofCertifiedPhysicianAssistants%206.27.pdf. Accessed July 2018.
3. National Commission on Certification of Physician Assistants. 2016 Statistical Profile of Certified Physician Assistants. https://prodcmsstoragesa.blob.core.windows.net/uploads/files/2016StatisticalProfilebySpecialty.pdf. Accessed July 2018.

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]

Merle L. Diamond, MD, Director of Diamond Headache Clinic, Clinical Assistant Professor, Rosalind Franklin University of Medicine and Science, Chicago Medical School, Chicago, IL

Susan Hutchinson, MD, Director of Orange County Migraine & Headache Center, Irvine, CA

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.; Pernix 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.; Pernix Therapeutics; and Supernus Pharmaceuticals, Inc. She has participated in research studies for GlaxoSmithKline plc.

ACKNOWLEDGEMENT

Editorial support was provided by Gregory Scott, PharmD, RPh at the Primary Care Education Consortium.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from Lilly USA, LLC.

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.[12] 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).[13]

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)**.[14] The presence of a red flag does not confirm a secondary headache.[12]

The assessment for red flags begins with a detailed history and physical and neurological examination.[14] 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.[15,16] 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.[15,16] Magnetic resonance imaging is the preferred method of imaging in nonacute headache.[16] 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.[16] 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**.[17]

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.[18]

FIGURE Ruling out secondary causes of headache: SNOOP4[14]

S	ystemic symptoms/signs/disease
N	eurologic symptoms or signs
O	nset sudden
O	nset after age 50 years
P	attern change (if previous history) • Progressive headache with loss of headache-free periods • Precipitated by Valsalva maneuver • Postural aggravation • Papilledema

Figure: © Georg Thieme Verlag KG.

Patients may have more than one type of primary headache.[13] 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 (**TABLE 2**).[13]

For example, migraine is unilateral in approximately 54% to 67% of patients.[19] Similarly, only about 13% to 41% of patients with migraine experience aura.[19] 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.[20]

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.[13]

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.[13] In addition, the frequency, signs and symptoms, and associated disability of migraine may vary over time, even within the same day.[13]

TABLE 1 Important characteristics to assess as part of the headache history[17]

Pattern—when and how it begins; continuous, episodic, or both
Triggers
Duration
Nature—location, character, severity
Premonitory symptoms, eg, excessive tiredness; yawning; excessive urination; neck stiffness; vertigo; visual/auditory
Symptoms accompanying attack, eg, nausea, sensitivity to lights, noises, smells, touch, movement
Treatments—current and previous; when taken; if effective or abandoned
Previous medical history—depression; sleep disorders; allergies
Current medications
Family history, especially of headache
Social history—occupation; smoking; alcohol and tobacco consumption
Previous medical consultation

TABLE 2 ICHD-3 diagnostic criteria for: 1.1 migraine without aura headache[13]

A	≥5 attacks[a] fulfilling criteria B-D
B	Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated)[b,c]
C	Headache has ≥2 of the following 4 characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by, or causing avoidance of, routine physical activity, eg, walking or climbing stairs
D	During headache ≥1 of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia
E	Not better accounted for by another ICHD-3 diagnosis

Abbreviations: ICHD-3, International Classification of Headache Disorders, 3rd edition.

[a]One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least 5 attacks are required. Individuals who otherwise meet criteria for 1.1 Migraine without Aura but have had fewer than 5 attacks should be coded 1.5.1 Probable Migraine without Aura.

[b]When the patient falls asleep during a migraine attack and wakes up without it, duration of the attack is reckoned until the time of awakening.

[c]In children and adolescents (age <18 years), attacks may last 2-72 hours (the evidence for untreated durations of <2 hours in children has not been substantiated).

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.[13] 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.[21,22]

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.[21] 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.[11] 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%).[23] Triptan use was highest in the maximum efficacy group, while opioid or barbiturate use was highest in the moderate and poor efficacy groups.[23]

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."[13] 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.[24] 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.[25] Among these, a three-item subset assessing disability, nausea, and photophobia

TABLE 3 ID Migraine Test[25]

_____	You felt nauseated or sick to your stomach
_____	How many days did your headache limit you from working, studying, or doing what you needed to do?
_____	Light bothered you (a lot more than when you don't have headaches)

(**TABLE 3**) provided optimum 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 (eg, light, stress, caffeine, alcohol) from nonmodifiable (menstruation for females, environmental) factors, targeting treatment at those that are modifiable. Diaries are available from several sources:

- American Academy of Family Physicians (https://www.aafp.org/fpm/2013/0500/fpm20130500p24-rt1.pdf)
- Migraine Trust (https://www.migrainetrust.org/wp-content/uploads/2015/11/FS05aMigraineDiaries.pdf)
- National Headache Foundation (https://headaches.org/wp-content/uploads/2018/02/Diary2.pdf) ●

REFERENCES

1. Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache.* 2001;41(7):646-657.
2. Burch RC, Loder S, Loder E, et al. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. *Headache.* 2015;55(1):21-34.
3. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 2017;390(10100):1211-1259.
4. Lampl C, Thomas H, Stovner LJ, et al. Interictal burden attributable to episodic headache: findings from the Eurolight project. *J Headache Pain.* 2016;17:9.
5. Schurks M, Rist PM, Bigal ME, et al. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ.* 2009;339:b3914.
6. Kurth T, Winter AC, Eliassen AH, et al. Migraine and risk of cardiovascular disease in women: prospective cohort study. *BMJ.* 2016;353:i2610.
7. Seng EK, Buse DC, Klepper JE, et al. Psychological factors associated with chronic migraine and severe migraine-related disability: An observational study in a tertiary headache center. *Headache.* 2017;57(4):593-604.
8. Oh K, Cho SJ, Chung YK, et al. Combination of anxiety and depression is associated with an increased headache frequency in migraineurs: a population-based study. *BMC Neurol.* 2014;14:238.
9. Payne KA, Varon SF, Kawata AK, et al. The International Burden of Migraine Study (IBMS): study design, methodology, and baseline cohort characteristics. *Cephalalgia.* 2011;31(10):1116-1130.
10. Buse DC, Powers SW, Gelfand AA, et al. Adolescent perspectives on the burden of a parent's migraine: results from the CaMEO study. *Headache.* 2018;doi:10.1111/head.13254.
11. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology.* 2007;68(5):343-349.
12. Bigal ME, Lipton RB. The differential diagnosis of chronic daily headaches: an algorithm-based approach. *J Headache Pain.* 2007;8(5):263-272.
13. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia.* 2018;38(1):1-211.
14. Dodick DW. Pearls: headache. *Semin Neurol.* 2010;30(1):74-81.
15. Mitsikostas DD, Ashina M, Craven A, et al. European Headache Federation consensus on technical investigation for primary headache disorders. *J Headache Pain.* 2015;17:5.
16. Holle D, Obermann M. The role of neuroimaging in the diagnosis of headache disorders. *Ther Adv Neurol Disord.* 2013;6(6):369-374.
17. Weatherall MW. The diagnosis and treatment of chronic migraine. *Ther Adv Chronic Dis.* 2015;6(3):115-123.
18. Probyn K, Bowers H, Caldwell F, et al. Prognostic factors for chronic headache: A systematic review. *Neurology.* 2017;89:291-301.
19. Bigal ME, Liberman JN, Lipton RB. Age-dependent prevalence and clinical features of migraine. *Neurology.* 2006;67(2):246-251.
20. Reed ML, Fanning KM, Serrano D, et al. Persistent frequent nausea is associated with progression to chronic migraine: AMPP study results. *Headache.* 2015;55(1):76-87.
21. Lipton RB, Manack Adams A, Buse DC, et al. A comparison of the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study and American Migraine Prevalence and Prevention (AMPP) Study: Demographics and headache-related disability. *Headache.* 2016;56(8):1280-1289.
22. Bigal ME, Serrano D, Reed M, et al. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. *Neurology.* 2008;71(8):559-566.
23. Lipton RB, Fanning KM, Serrano D, et al. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. *Neurology.* 2015;84(7):688-695.
24. Tepper SJ, Dahlof CG, Dowson A, et al. Prevalence and diagnosis of migraine in patients consulting their physician with a complaint of headache: data from the Landmark Study. *Headache.* 2004;44(9):856-864.
25. Lipton RB, Dodick D, Sadovsky R, et al. A self-administered screener for migraine in primary care: The ID Migraine validation study. *Neurology.* 2003;61(3):375-382.

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

Paul P. Doghramji, MD, FAAFP

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.

DISCLOSURES

As a continuing medical education provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), Primary Care Education Consortium (PCEC) requires any individual in a position to influence educational content to disclose any financial interest or other personal relationship with any commercial interest. This includes any entity producing, marketing, reselling or distributing health care goods or services consumed by, or used on, patients. Mechanisms are in place to identify and resolve any potential conflict of interest prior to the start of the activity. In addition, any discussion of off-label, experimental, or investigational use of drugs or devices will be disclosed by the faculty.

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

Gregory Scott, PharmD, RPh and Angela Cimmino, PharmD, editorial support, disclose they have no real or apparent conflicts of interest to report.

Michael Hanak, MD, CME Reviewer, discloses that he has no real or apparent conflicts of interest to report.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium

ACCREDITATION

The Primary Care Education Consortium is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

CREDIT DESIGNATION

AMA PRA Category 1 – Primary Care Education Consortium designates this activity for a maximum of 1.0 AMA PRA Category 1 credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Release Date: 1 August 2018
Expiration Date: 31 July 2019

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
AAPA accepts certificates of participation of educational activities certified for AMA PRA Category 1 Credit™ from organizations accredited by ACCME or a recognized state medical society.

SUPPORTER

This article is supported by an educational grant from Ironwood Pharmaceuticals, Inc.

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

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

ACKNOWLEDGEMENT
Editorial support was provided by Gregory Scott, PharmD, RPh, and Angela Cimmino, PharmD. The author was responsible for all content and editorial decisions.

SUPPORT
This article is sponsored by Primary Care Education Consortium and supported by funding from Ironwood Pharmaceuticals, Inc.

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 midfoot, 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.

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/m^2) 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.[9] 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.[12,14] 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.[14] 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.[12,15]

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-

TABLE **Key studies of urate-lowering therapy**[18,19,22-25]

• Study/author • Baseline sUA level • Prior treatment	Treatment	Primary efficacy result
• FACT/Becker[18] • Mean sUA, 9.8-9.9 mg/dL • ALP (44% of subjects)	*52 weeks* ALP 300 mg/d (n=253) FBX 80 mg/d (n=256) FBX 120 mg/d (n=251)	*Percentage of patients with sUA <6 mg/dL at last 3 monthly measurements* ALP 300 mg/d: 21% FBX 80 mg/d: 53% (*P*<.001)[a] FBX 120 mg/d: 62% (*P*<.001)[a]
• APEX/Schumacher[19] • Mean sUA, 9.85 mg/dL • ALP (~1/3 of subjects)	*28 weeks* ALP 300 mg/d (n=268)[b] FBX 80 mg/d (n=267) FBX 120 mg/d (n=269) FBX 240 mg/d (n=134) PBO (n=134)	*Percentage of patients with sUA <6 mg/dL at last 3 monthly measurements* ALP 300 mg/d: 22% FBX 80 mg/d: 48% (*P*≤.05)[a] FBX 120 mg/d: 65% (*P*≤.05)[a] FBX 240 mg/d: 69% (*P*≤.05)[a] PBO: 0%
• CLEAR 1/Saag[23] • sUA, ≥6.5 mg/dL • ALP ≥300 mg/d (≥200 mg/d in patients with moderate renal impairment) and ≥2 gout flares during the previous year	*12 months* PBO/ALP (n=201) LSN 200 mg/d +ALP (n=201) LSN 400 mg/d + ALP (n=201)	*Percentage of patients with sUA <6 mg/dL at 6 months* PBO/ALP: 27.9% LSN 200 mg/d + ALP: 54.2% (*P*<.0001)[a] LSN 400 mg/d + ALP: 59.2% (*P*<.0001)[a]
• CRYSTAL/Dalbeth[22] • ULT-naïve: sUA, ≥8 mg/dL; ULT treated: sUA, ≥6 mg/dL	*12 months* PBO/FBX 80 mg/d (n=109) LSN 200 mg/d + FBX 80 mg/d (n=106) LSN 400 mg/d + FBX 80 mg/d (n=109)	*Percentage of patients with sUA <5 mg/dL by month 6* PBO/FBX 80 mg/d: 46.8% LSN 200 mg/d + FBX 80 mg/d: 56.6% (*P*=.13)[a] LSN 400 mg/d + FBX 80 mg/d: 76.1% (*P*<.0001)[a]
• Open label study/Reinders[24] • N/A • Benzbromarone	*Stage 1: 2 months* ALP 200-300 mg/d (based on renal function) (n=32) *Stage 2: >2 months* Probenecid 1000 mg/d, added to ALP in patients failing to attain sUA <0.3 mmol/L[c] (n=14)	*Percentage of patients attaining sUA <0.3 mmol/L*[c] *Stage 1* ALP monotherapy: 25% *Stage 2* ALP plus probenecid: 86%
• CO405/Sundy[25] • sUA, 9.4-10.4 mg/dL • Intolerant or refractory to ALP	*6 months* Group 1: Pegloticase 8 mg biweekly (n=43) Group 2: Pegloticase 8 mg monthly (n=41) Group 3: Placebo (n=20)	*Percentage of patients with sUA <6 mg/dL ≥80% of the time at Month 3 and Month 6* Group 1: 47% (95% CI, 31%-62%) Group 2: 20% (95% CI, 9%-35%) Group 3: 0
• CO406/Sundy[25] • sUA, 9.5-9.8 mg/dL • Intolerant or refractory to ALP	*6 months* Group 1: Pegloticase 8 mg biweekly (n=42) Group 2: Pegloticase 8 mg monthly (n=43) Group 3: Placebo (n=23)	*Percentage of patients achieving sUA <6 mg/dL ≥80% of the time at Month 3 and Month 6* Group 1: 38% (95% CI, 24%-54%) Group 2: 49% (95% CI, 33%-65%) Group 3: 0

[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**).[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.[12,13,15] Febuxostat has been associated with cutaneous reactions, but data do not support any cross-reactivity with allopurinol.[12] Liver function abnormalities and a slightly higher incidence of cardiovascular thromboembolic events may occur.[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.[12,13,15] The efficacy of probenecid in combination with allopurinol in such patients has been demonstrated in a few small trials.[21] However, probenecid is not recommended in patients with a creatinine clearance <50 mL/minute or uric acid urolithiasis.[15]

Lesinurad is approved only as add-on therapy to a xanthine oxidase inhibitor.[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**).[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).[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.[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.[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.[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.[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.[12] 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.[15] Dosages of 600 to 800 mg/d have a 75% to 80% success rate in achieving an sUA level <6 mg/dL.[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.[12] ACR guidelines, however, recommend increasing allopurinol until the sUA target level is reached in these patients, while monitoring for drug toxicity.[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.[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.[20] ACR guidelines suggest uptitration to as much as 120 mg/d (an investigational dosage) if necessary to achieve the target sUA level.[15]

Probenecid

The initial dosage of probenecid is 250 mg twice daily, uptitrated weekly to 1 g twice daily, based on the sUA level.[6] Patients must be counseled to hydrate well due to the risk of urolithiasis.[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.[15]

Lesinurad

Lesinurad is indicated at a dosage of 200 mg/d as add-on therapy to allopurinol or febuxostat.[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.[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 inadvertently 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 other 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. ●

REFERENCES

1. Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. *BMC Med.* 2017;15(1):123.
2. Zhang Y, Peloquin CE, Dubreuil M, et al. Sleep apnea and the risk of incident gout: A population-based, body mass index-matched cohort study. *Arthritis Rheumatol.* 2015;67(12):3298-3302.
3. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. *Am J Med.* 2012;125(7):679-687.e1.
4. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum.* 2011;63(10):3136-3141.
5. MacFarlane LA, Kim SC. Gout: a review of nonmodifiable and modifiable risk factors. *Rheum Dis Clin North Am.* 2014;40(4):581-604.
6. Ragab G, Elshahaly M, Bardin T. Gout: An old disease in new perspective - A review. *J Adv Res.* 2017;8(5):495-511.
7. Ruoff G, Edwards NL. Overview of serum uric acid treatment targets in gout: Why less than 6 mg/dL? *Postgrad Med.* 2016;128(7):706-715.
8. Doghramji PP. Hot topics in primary care: Update on the recognition and management of gout: More than the great toe. *J Fam Pract.* 2015;64(12 Suppl):S31-S36.
9. Roddy E. Revisiting the pathogenesis of podagra: why does gout target the foot? *J Foot Ankle Res.* 2011;4(1):13.
10. Roddy E. Gout: presentation and management in primary care. In: *Hands On: Reports on the Rheumatic Diseases: Series 6, No 9.* Derbyshire, UK: Arthritis Research UK; 2011: 1-6.
11. Doherty M, Jansen TL, Nuki G, et al. Gout: why is this curable disease so seldom cured? *Ann Rheum Dis.* 2012;71(11):1765-1770.
12. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis.* 2017;76(1):29-42.
13. Sivera F, Andrés M, Carmona L, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative. *Ann Rheum Dis.* 2014;73(2):328-335.
14. Keenan RT. Limitations of the current standards of care for treating gout and crystal deposition in the primary care setting: a review. *Clin Ther.* 2017;39(2):430-441.
15. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken).* 2012;64(10):1431-1446.
16. Zurampic [package insert]. Wilmington, DE: AstraZeneca; 2016.
17. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther.* 2010;12(2):R63.
18. Becker MA, Schumacher HR Jr., Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med.* 2005;353(23): 2450-2461.
19. Schumacher HR, Jr., Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum.* 2008;59(11):1540-1548.
20. Uloric [package insert]. Deerfield, IL: Takeda Pharmaceuticals America; 2018.
21. Jones G, Panova E, Day R. Guideline development for the management of gout: role of combination therapy with a focus on lesinurad. *Drug Des Devel Ther.* 2017;11:3077-3081.
22. Dalbeth N, Jones G, Terkeltaub R, et al. Lesinurad, a selective uric acid reabsorption inhibitor, in combination with febuxostat in patients with tophaceous gout: Findings of a phase III clinical trial. *Arthritis Rheumatol.* 2017;69(9):1903-1913.
23. Saag KG, Fitz-Patrick D, Kopicko J, et al. Lesinurad combined with allopurinol: A randomized, double-blind, placebo-controlled study in gout patients with an inadequate response to standard-of-care allopurinol (a US-based study). *Arthritis Rheumatol (Hoboken, NJ).* 2017;69(1):203-212.
24. Reinders MK, van Roon EN, Houtman PM, Brouwers JR, Jansen TL. Biochemical effectiveness of allopurinol and allopurinol-probenecid in previously benzbromarone-treated gout patients. *Clin Rheumatol.* 2007;26(9):1459-1465.
25. Sundy JS, Baraf HS, Yood RA, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *JAMA.* 2011;306(7):711-720.
26. Dalbeth N, Kumar S, Stamp L, Gow P. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J Rheumatol.* 2006;33(8):1646-1650.
27. Stamp LK, O'Donnell JL, Zhang M, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. *Arthritis Rheum.* 2011;63(2):412-421.
28. Vázquez-Mellado J, Morales EM, Pacheco-Tena C, Burgos-Vargas R. Relation between adverse events associated with allopurinol and renal function in patients with gout. *Ann Rheum Dis.* 2001;60(10):981-983.
29. Duzallo [package insert]. Cambridge, MA: Ironwood; 2017.
30. Krystexxa [package insert]. Lake Forest, IL: Horizon Pharma USA; 2016.

Individualizing Treatment with Statin Therapy

Harold Edward Bays, MD, FOMA, FTOS, FACC, FACE, FNLA; Michael Cobble, MD, FNLA

LEARNING OBJECTIVES

After participating, the clinician will be able to:

- Clarify the role of statins in the treatment of elevated low-density lipoprotein cholesterol (LDL-C) according to current guidelines and other recommendations
- Individualize statin therapy based on patient needs and characteristics

INTRODUCTION

Statin therapy remains the pharmacological foundation for the management of elevated low-density lipoprotein cholesterol (LDL-C). This is due to an established record of safety with lowering LDL-C, and supported by a host of outcome trials indicating a significant reduction in major cardiovascular (CV) events.[1] Yet, many challenges and questions still 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

Harold Edward Bays, MD, FOMA, FTOS, FACC, FACE, FNLA
Medical Director / President
Louisville Metabolic and Atherosclerosis Research Center
Louisville, Kentucky

Michael Cobble, MD, FNLA
Diplomate, American Board of Clinical Lipidology
Certified Hypertension Specialist
Adjunct Faculty, University of Utah School of Medicine,
Salt Lake City, Utah

DISCLOSURES

Dr. Bays discloses that he is on the advisory boards for Alnylam Pharmaceuticals, Inc.; Akcea Therapeutics; Amgen Inc.; AstraZeneca; Eisai Co., Ltd.; Eli Lilly and Company; Esperion; Ionis Pharmaceuticals (ISIS); Janssen Pharmaceuticals, Inc.; Johnson & Johnson; Kowa Pharmaceuticals America, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; ProSciento; Regeneron Pharmaceuticals, Inc.; and sanofi-aventis U.S. LLC. He is on the speakers' bureaus for Amarin Corporation; Amgen Inc.; Eisai Co., Ltd.; Kowa Pharmaceuticals America, Inc.; Orexigen Therapeutics, Inc.; Regeneron Pharmaceuticals, Inc.; and sanofi-aventis U.S. LLC.

Dr. Cobble discloses that he is on the advisory board for Kowa Pharmaceuticals America, Inc. and on the speakers' bureaus for Amarin Corporation; Amgen Inc.; AstraZeneca; Kowa Pharmaceuticals America, Inc.; Regeneron Pharmaceuticals, Inc.; and sanofi-aventis U.S. LLC.

ACKNOWLEDGEMENT

Editorial support was provided by Gregory Scott, PharmD, RPh and James Backes, PharmD. The authors were responsible for all content and editorial decisions.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from Kowa Pharmaceuticals America, Inc.

TABLE 1 Comparative highlights of major lipid guidelines and recommendations

ACC/AHA[1] 2013	NLA[2] 2014	USPSTF[4] 2016	AACE/ACE[3] 2017
All guidelines recommend lifestyle as the foundation for ASCVD risk reduction			
Shifted away from LDL-C goals **Statin-intensity** categories • High-intensity ≥50% LDL-C ↓ • Moderate-intensity 30 to <50% LDL-C ↓ • Low-intensity <30% LDL-C ↓ Four statin benefit groups – patients with: 1. Any form of clinical ASCVD *Primary prevention* 2. LDL-C ≥ 190[a] 3. (+) DM, 40-75 yrs of age with LDL-C 70-189[a] 4. (-) DM, 40-75 yrs of age + estimated 10-y ASCVD risk ≥7.5% Introduced ASCVD risk calculator • Added race, gender, presence of DM, and treatment for hypertension to risk calculation; along with lifetime risk of ASCVD • Predicts 10-y ASCVD risk for primary prevention patients • Guides statin intensity for patients with 10-y risk of 5 to <7.5% and ≥7.5%	**Primary targets: non-HDL-C[c] and LDL-C** Recommended moderate- or high-intensity statin Treatment goals: (mg/dL) Risk / non-HDL-C[a,c] / LDL-C[a] Low: <130 / <100 Moderate: <130 / <100 High: <130 / <100 Very high: <100 / <70 Criteria for ASCVD risk assessment Risk / Criteria Low: 0-1 ASCVD RFs[b] Moderate: 2 ASCVD RFs[b] High: ≥3 ASCVD RFs[b] *or* DM + (0-1 ASCVD RFs[b] *or* stage 3B/4 CKD *or* LDL-C ≥190 mg/dL) Very high: ASCVD DM + (≥2 ASCVD RFs[b] *or* end organ damage)	*Primary prevention* Age 40-75 y with no history of CVD, ≥1 CVD risk factor, and estimated 10-y ASCVD risk 7.5%-10%: selectively offer low- to moderate-dose statin Age 40-75 y with no history of CVD, ≥1 CVD risk factor, and estimated 10-y ASCVD risk ≥10%: initiate low- to moderate-dose statin Age ≥76 y with no history of CVD: no recommendation due to insufficient evidence LDL-C >190 mg/dL: may require statin use Familial hypercholesterolemia: may require statin use	**Primary targets: LDL-C and non-HDL-C[c]** Endorsed 10-yr ASCVD risk prediction using various assessment calculators Statins are recommended as the primary drug therapy for achieving LDL-C goals Introduced 'extreme risk' category and aggressive lipid targets – patients with: • Progressive ASCVD despite LDL-C <70[a] • ASCVD + DM, CKD (Stages 3/4) *or* HeFH • History of premature ASCVD Lipid targets: • LDL-C <55[a] • Non-HDL-C <80[a,c]

[a]mg/dL

[b]Major risk factors = age (male ≥45 y, female ≥55 y), family history of early ASCVD (<55 y of age in a male first-degree relative or <65 y in a female first-degree relative), (+) cigarette smoking, high blood pressure (≥140/90 mm Hg, or on blood pressure medication), and low HDL-C (male <40 mg/dL, female <50 mg/dL).

[c]non-HDL-C = total cholesterol – HDL-C

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, American College of Endocrinology; ACS, acute coronary syndrome; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetSyn, metabolic syndrome; NLA, National Lipid Association; REs, risk equivalents; RFs, risk factors; y, year.

(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**).[2] 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.[1] 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

TABLE 2 Statin-intensity categories[1]

High-intensity — dosed daily (↓ LDL-C ≥50%)	Moderate-intensity — dosed daily (↓ LDL-C 30 to <50%)	Low-intensity — dosed daily (↓ LDL-C <30%)
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Fluvastatin 40 mg bid	Pravastatin 10-20 mg
	Fluvastatin XL 80 mg	Lovastatin 20 mg
	Lovastatin 40 mg	Fluvastatin 20-40 mg
	Pitavastatin 2-4 mg	Pitavastatin 1 mg
	Pravastatin 40-80 mg	
	Rosuvastatin 5-10 mg	
	Simvastatin 20-40 mg	

Abbreviations: bid, twice daily; LDL-C, low-density lipoprotein-cholesterol.

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.[5,6] Safety and tolerability are important considerations for statin therapy since, whether real or perceived, AEs are the primary reason for statin discontinuation.[7] This is important since statin discontinuation is associated with higher rates of ASCVD.[8] 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.[9,10]

When statin therapy results in a major AE, an underlying DI is frequently implicated. Drug interactions are well established with the individual statins.[11,12] 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).[12] 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.[12]

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."[13] Switching to another statin is also an option.

Statin intolerance due to musculoskeletal complaints typically involves myalgias or myopathy, with the latter being associated with elevated creatine kinase (CK) levels. In most instances, patients report myalgias, with normal CK values.[14] The incidence of statin-associated muscle symptoms (SAMS) is widely variable and not well-defined, but is estimated to affect approximately 15% of statin users.[13]

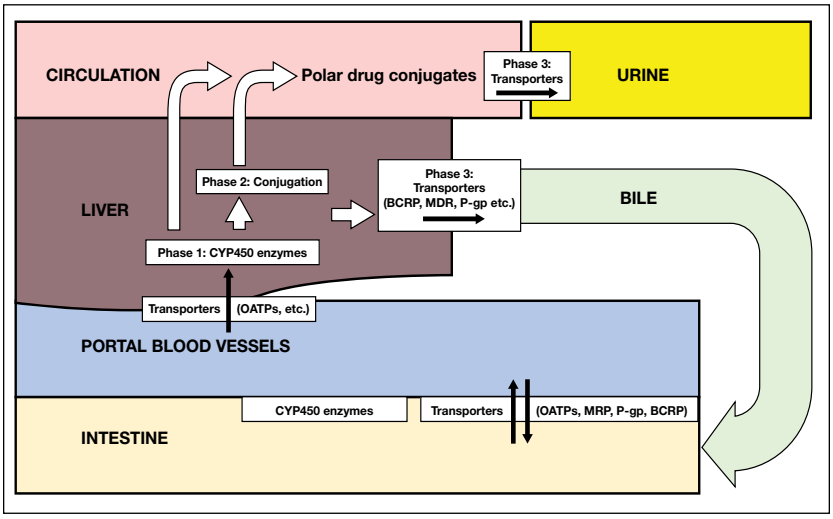
Statin intolerance can frequently be attributed to patient perception or other underlying medical conditions, comorbidities, and concomitant therapies. Nonetheless, there are certain patients that have a true sensitivity and are unable to tolerate any level of statin therapy.[5] However, before a patient is considered statin intolerant, the exclusion of other potential causes of muscle-related symptoms (eg, hyperuricemia, hypothyroidism, vitamin B_{12} and/or D deficiency, inflammatory diseases, and non-statin-related musculoskeletal disorders)[14] is warranted.

Muscle-associated symptoms or injury

The primary barrier to statin therapy is patient-reported musculoskeletal complaints.[14] 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.[15] 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),[14] which has recently been revised.[16] 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-

FIGURE **Steps involving statin metabolism.**



Phase 1 drug metabolism: Oxidation, reduction, and/or hydrolysis via cytochrome P450 enzymes

Phase 2 drug metabolism: Conjugation via glucuronidation, acetylation, glutathione conjugation, sulfate conjugation, methylation

Phase 3 drug metabolism: Distribution and elimination of drugs mediated by transporters

Cytochrome P450 enzymes (CYP450) = via microsomal/endoplasmic reticulum; most common CYP450 isoenzyme for drug metabolism is CYP450 3A4

Organic Anion-Transporting Polypeptides (OATP) = Organic anion-transporting polypeptides, including OATP1B1, facilitate drug movement in and out of intestinal cells and into liver cells; organic cationic transporters facilitate drugs movement in and out of the intestinal cells, and from the blood into the intestine and into the liver

Multidrug-Resistant-associated Proteins (MRP) = facilitate drug movement from intestinal cells into the blood

P-glycoproteins (P-gp) = facilitate drug movement from intestinal cells into the intestinal lumen, and from the liver into the bile

Breast Cancer-Resistant Proteins (BCRP) = facilitates drug movement from intestinal cells into the intestinal lumen, and from the liver into the bile

astatin, rosuvastatin, pitavastatin), and gradually titrating as tolerated from once-weekly to every other day dosing.[5] Finally, having frank discussions and incorporating shared decision-making when rechallenging patients with an alternative statin or dosing strategy are essential.[5]

Hepatotoxicity

The potential for hepatotoxicity with lipid-altering agents has historically been a concern for clinicians and, more recently, patients.[17] However, in 2012, the FDA removed the need for routine periodic monitoring of hepatic enzymes in all statin labeling.[9] 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.[18] 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.[17]

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 (**FIGURE**). 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.[12]

Approximately 75% of all medications are metabolized via the CYP450 system, with 50% of these agents having affinity for the CYP3A4 isoenzyme.[11] Lovastatin, simvastatin, and to a lesser extent, atorvastatin, are metabolized via CYP3A4. Concomitant use of strong CYP3A4 inhibitors, including azole antifungals, amiodarone, HIV protease inhibitors, certain macrolides (clarithromycin) and calcium channel blockers (amlodipine, diltiazem, and verapamil), and grapefruit juice, have the potential to markedly increase the serum concentrations of these statins.[12] Conversely, the statins that do not utilize the CYP3A4 isoenzyme for metabolism include fluvastatin, rosuvastatin, pitavastatin, and pravastatin. Moreover, the statins that are not dependent on the CYP450 system

for their metabolism are pitavastatin and pravastatin and thus, may have a reduced potential for significant DIs.[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.[12] All statins are substrates for OATP1B1 (**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.[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.[1] For those with HIV and taking protease inhibitors, the FDA has provided guidance on the use of statins to limit DIs.[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.[20] Epidemiologic data indicate that those with HIV infection have a 2-fold increased rate of CV events relative to non-infected patients.[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).[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,[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.[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.[22] A subsequent meta-analysis confirmed this small but significant link as statin therapy was associated with a 9% increased risk for incident DM.[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.[24] In 2013, a comprehensive meta-analysis further confirmed a dose-dependent link with NOD and a gradient of risk across many different individual statins.[25] Overall, most data indicate a modest increase in NOD (10%-12%) with several statin therapies, particularly among those at risk for DM.[26] 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.[23] Conversely, a few observational studies note higher rates and a stronger correlation, suggesting that deprescribing statin therapy in certain populations (ie, women age >75 years) may be advisable.[27,28]

The FDA considers statin-associated NOD a class effect,[9] but most data suggest the link is secondary to dose and each statin.[26] Zaharan et al found significantly higher rates of NOD with atorvastatin (HR, 1.25; *P*<.0001), rosuvastatin (HR, 1.42; *P*<.0001) and simvastatin (HR, 1.14; *P*=.0005) compared to pravastatin (HR, 1.02; *P*=NS) and fluvastatin (HR, 1.04; *P*=NS).[29] A meta-analysis of pitavastatin RCTs, including doses up to 8 mg daily, found no adverse effect on glucose metabolism or NOD.[30]

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 years who experienced notable, but ill-defined memory loss or impairment that was reversible upon discontinuation of statin therapy."[9]

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.[31,32] For example, an analysis of a possible association between statins and Alzheimer's disease among Medicare beneficiaries (N=399,979)[32] showed that patients with high statin exposure had a significantly lower risk of developing Alzheimer's disease (HR, 0.85-0.88; *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

1. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation*. 2014;63(25):2889-2934.
2. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 1&2. *J Clin Lipidol*. 2014;9(2):129-169.
3. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocr Pract*. 2017;23(Suppl 2):1-87.
4. United States Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults. US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016;316(19):1997-2007.
5. Backes JM, Ruisinger JF, Gibson CA, Moriarty PM. Statin-associated muscle symptoms-Managing the highly intolerant. *J Clin Lipidol*. 2017;11(1):24-33.
6. Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA*. 2004;292(21):2585-2590.
7. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): An internet-based survey of 10,138 current and former statin users. *J Clin Lipidol*. 2012;6(3):208-215.
8. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J*. 2013;34(38):2940-2948.
9. US Food and Drug Administration. FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs. Published 2012. https://www.fda.gov/Drugs/DrugSafety/ucm293101.htm. Accessed November 28, 2017.
10. Jacobson TA. NLA Task Force on Statin Safety--2014 update. *J Clin Lipidol*. 2014;8(3 Suppl):S1-S4.
11. Bottorff MB. Statin safety and drug interactions: clinical implications. *Am J Cardiol*. 2006;97(8a):27c-31c.
12. Kellick KA, Bottorff M, Toth PP. A clinician's guide to statin drug-drug interactions. *J Clin Lipidol*. 2014;8(3 Suppl):S30-S46.
13. Guyton JR, Bays HE, Grundy SM, Jacobson TA. An assessment by the Statin Intolerance Panel: 2014 update. *J Clin Lipidol*. 2014;8(3 Suppl):S72-S81.
14. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8(3 Suppl):S58-S71.
15. Rosenson RS, Baker S, Banach M, et al. Optimizing cholesterol treatment in patients with muscle complaints. *J Am Coll Cardiol*. 2017;70(10):1290-1301.
16. Rosenson RS, Miller K, Bayliss M, et al. The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI): Revision for clinical use, content validation, and inter-rater reliability. *Cardiovasc Drugs Ther*. 2017;31(2):179-186.
17. Bays H, Cohen DE, Chalasani N, Harrison SA. An assessment by the statin liver safety task force: 2014 update. *J Clin Lipidol*. 2014;8(3):S47-S57.
18. Goldberg DS, Forde KA, Carbonari DM, et al. Population-representative incidence of drug-induced acute liver failure based on an analysis of an integrated health care system. *Gastroenterology*. 2015;148(7):1353-1361.e1353.
19. US Food and Drug Administration. FDA Drug Safety Communication: Interactions between certain HIV or heptatitis C drugs and cholesterol-lowering statin drugs can increase the risk of muscle injury. Published 2012. https://www.fda.gov/Drugs/DrugSafety/ucm293877.htm. Accessed November 28, 2017.
20. Triant VA. Cardiovascular disease and HIV infection. *Curr HIV/AIDS Rep*. 2013;10(3):199-206.
21. ClinicalTrials.gov. Evaluating the use of pitavastatin to reduce the risk of cardiovascular disease in hiv-infected adults (REPRIEVE). Published 2015. https://clinicaltrials.gov/ct2/show/NCT02344290. Accessed November 29, 2017.
22. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207.
23. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375(9716):735-742.
24. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011;305(24):2556-2564.
25. Navarese EP, Buffon A, Andreotti F, et al. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. *Am J Cardiol*. 2013;111(8):1123-1130.
26. Maki KC, Ridker PM, Brown WV, Grundy SM, Sattar N, The Diabetes Subpanel of the National Lipid Association Expert P. An assessment by the Statin Diabetes Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8(3 Suppl):S17-S29.
27. Jones M, Tett S, Peeters GMEE, Mishra GD, Dobson A. New-onset diabetes after statin exposure in elderly women: the Australian longitudinal study on women's health. *Drugs Aging*. 2017;34(3):203-209.
28. Mansi I, Frei CR, Wang CP, Mortensen EM. Statins and new-onset diabetes mellitus and diabetic complications: A retrospective cohort study of US healthy adults. *J Gen Intern Med*. 2015;30(11):1599-1610.
29. Zaharan NL, Williams D, Bennett K. Statins and risk of treated incident diabetes in a primary care population. *Br J Clin Pharmacol*. 2013;75(4):1118-1124.
30. Vallejo-Vaz AJ, Kondapally Seshasai SR, Kurogi K, et al. Effect of pitavastatin on glucose, HbA_{1c} and incident diabetes: A meta-analysis of randomized controlled clinical trials in individuals without diabetes. *Atherosclerosis*. 2015;241(2):409-418.
31. Swiger KJ, Martin SS, Tang F, et al. Cognitive and physical function by statin exposure in elderly individuals following acute myocardial infarction. *Clin Cardiol*. 2015;38(8):455-461.
32. Zissimopoulos JM, Barthold D, Brinton R, Joyce G. Sex and race differences in the association between statin use and the incidence of alzheimer disease. *JAMA Neurology*. 2017;74(2):225-232.

Advances in Type 2 Diabetes: Focus on Basal Insulin/Glucagon-Like Peptide-1 Receptor Agonist Combination Therapy

Jay H. Shubrook, DO, FAAFP, FACOFP

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).[6] 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

Jay H. Shubrook, DO, FAAFP, FACOFP, Professor, Primary Care Department, Director of Clinical Research and Diabetes Services, Touro University, California College of Osteopathic Medicine, Vallejo, California

DISCLOSURES

Dr. Shubrook discloses that he is on the advisory boards for Intarcia Therapeutics, Inc.; Lilly Diabetes; and Novo Nordisk Inc.

ACKNOWLEDGEMENT

Editorial support was provided by Gregory Scott, PharmD, RPh. The author was responsible for all content and editorial decisions.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from Sanofi US.

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).[12-18] The short-acting GLP-1RAs (exenatide twice-daily and lixisenatide), which slow gastric emptying, produce strong reduction of PPG and modest reduction of FPG.[12,13,19] The GLP-1RAs also suppress appetite, producing modest weight loss of 1 to 2 kg in most patients with T2DM.[20,21]

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.[22] 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.[23] 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.[24] 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).[25]

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.[26,27] Historically, to normalize the PPG, rapid- or short-acting prandial insulin has been added to basal insulin.[28,29] 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.[8] 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.[30] After a 12-week period to optimize the dose of insulin glargine

(mean dose 61 units/d), patients with A1c >7.0% (N=627) were randomized to exenatide 5 to 10 mcg twice daily or insulin lispro 3 times per day titrated to achieve a premeal glucose concentration of 100 to 108 mg/dL. After 30 weeks, the A1c was reduced to 7.2% and 7.1% in the exenatide and lispro groups, respectively, down from randomization A1c values of 8.3% and 8.2% (end of treatment difference -0.04%; 95% CI, -0.18-0.11). From a randomized FPG of 128 mg/dL for both groups, the FPG was 117 and 130 mg/dL at study end in the exenatide and lispro groups, respectively (*P*=.002). Reductions in PPG were similar in both groups except after lunch, in which the reduction with lispro was greater than with exenatide (-56 vs -39 mg/dL; *P*<.001).

Other randomized controlled trials investigating the addition of albiglutide or lixisenatide to basal insulin have shown similar results when compared with the addition of prandial insulin.[31,32]

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.[33] 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.[34] 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).[35,36] 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.

INSULIN GLARGINE/LIXISENATIDE

LixiLan-O trial

The LixiLan-O trial compared the individual components of glargine U-100 and lixisenatide with the fixed-ratio product IGlarLixi in patients with T2DM inadequately controlled with metformin with or without a second oral medication (N=1170).[37] At the end of 30 weeks, from a baseline of 8.1%, the A1c was reduced -1.6% with IGlarLixi compared with -1.3% for glargine and -0.9% for lixisenatide 20 mcg/d (*P*<.0001 IGlarLixi vs comparators). The reduction in FPG was similar with IGlarLixi (-63 mg/dL) and glargine (-59 mg/dL) and smaller with lixisenatide 20 mcg/d (-27 mg/dL; *P*<.0001 vs IGlarLixi). The reduction in PPG was greater with IGlarLixi (-103 mg/dL) than glargine (-59 mg/dL; 95% CI, -2.8 to -2.0) or lixisenatide (-83 mg/dL; 95% CI, -1.6 to -0.6). The total daily dose of insulin at study end was 39.8 units with IGlarLixi and 40.3 units with glargine.

Changes in body weight were as expected, with a -0.3 kg loss with IGlarLixi. The rate of symptomatic hypoglycemia (≤70 mg/dL) was highest with IGlarLixi at 1.4 events/patient-year, compared with glargine at 1.2 events/patient-year and lixisenatide at 0.3 events/patient-year. Nausea (9.6% vs 24.0%) and vomiting (3.2% vs 6.4%) occurred less frequently with IGlarLixi than lixisenatide, respectively, likely due to the slow increase in lixisenatide dose due to titration of the insulin dose. A positively adjudicated major adverse cardiovascular event occurred in 2 patients in the IGlarLixi group, 7 patients in the glargine group, and 2

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 patients treated with IGlarLixi achieved A1c <7% without weight gain and documented symptomatic hypoglycemia, compared with 9% of glargine patients (P<.0001).[38]

Post hoc analyses

Further analyses of LixiLan-O, LixiLan-L, and other trials demonstrated additional benefits of IGlarLixi compared with glargine. In LixiLan-L, an A1c <7% was achieved by 50% 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 liraglutide 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 liraglutide (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 liraglutide (-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 liraglutide, 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 liraglutide (0.2 events/patient-year). Nausea occurred less frequently with IDegLira than liraglutide (9% vs 20%), likely because of the slow increase in liraglutide 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 liraglutide groups. Two cases of treatment-emergent pancreatitis occurred in the liraglutide 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/m^2).

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 m^2).[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.[35] 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.[35] 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).[36] 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. ●

REFERENCES

1. Carls G, Huynh J, Tuttle E, Yee J, Edelman SV. Achievement of glycated hemoglobin goals in the US remains unchanged through 2014. *Diabetes Ther*. 2017;8(4):863-873.
2. Wong ND, Patao C, Wong K, Malik S, Franklin SS, Iloeje U. Trends in control of cardiovascular risk factors among US adults with type 2 diabetes from 1999 to 2010: comparison by prevalent cardiovascular disease status. *Diab Vasc Dis Res*. 2013;10(6):505-513.
3. Yu S, Schwab P, Bian B, Radican L, Tunceli K. Use of add-on treatment to metformin monotherapy for patients with type 2 diabetes and suboptimal glycemic control: a U.S. database study. *J Manag Care Spec Pharm*. 2016;22(3):272-280.
4. Blonde L, Meneghini L, Boss A, et al. Real-world observational study to evaluate probability of achieving glycaemic control in patients with type 2 diabetes. International Diabetes Federation Congress; December 4-8, 2017; Abu Dhabi, United Arab Emirates.
5. Dalal MR, Grabner M, Bonine N, Stephenson JJ, DiGenio A, Bieszk N. Are patients on basal insulin attaining glycemic targets? Characteristics and goal achievement of patients with type 2 diabetes mellitus treated with basal insulin and physician-perceived barriers to achieving glycemic targets. *Diabetes Res Clin Pract*. 2016;121: 17-26.
6. Mauricio D, Meneghini L, Seufert J, et al. Glycaemic control and hypoglycaemia burden in patients with type 2 diabetes initiating basal insulin in Europe and the USA. *Diabetes Obes Metab*. 2017;19(8):1155-1164.
7. Khunti K, Nikolajsen A, Thorsted BL, Andersen M, Davies MJ, Paul SK. Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. *Diabetes Obes Metab*. 2016;18(4):401-409.
8. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(suppl 1):S73-S85.
9. Zisman A. The BeAM factor: An easy-to-determine, objective, clinical indicator for when to add prandial insulin vs continued basal insulin titration. Paper presented at: American Diabetes Association 71st Scientific Sessions; June 24-28, 2011; San Diego, CA.
10. Shaefer C, Traylor L, Gao L, Dex T, Sepe P, Skolnik N. Exploratory study of a dose-response curve for basal insulin. Presented at: American Diabetes Association 75th Scientific Session; June 5-9, 2015; Boston, MA.

11. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2018 executive summary. *Endocr Pract*. 2018;24(1):91-120.
12. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet*. 2008;372(9645):1240-1250.
13. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet*. 2009;374(9683):39-47.
14. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2013;381(9861):117-124.
15. Pratley RE, Nauck MA, Barnett AH, et al. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. *Lancet Diabetes Endocrinol*. 2014;2(4):289-297.
16. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care*. 2014;37(8):2159-2167.
17. Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet*. 2014;384(9951):1349-1357.
18. Nauck MA, Petrie JR, Sesti G, et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with type 2 diabetes. *Diabetes Care*. 2016; 39(2):231-241.
19. Rosenstock J, Raccah D, Koranyi L, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). *Diabetes Care*. 2013;36(10):2945-2951.
20. Sun F, Chai S, Li L, et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss in patients with type 2 diabetes: a systematic review and network meta-analysis. *J Diabetes Res*. 2015;2015:157201.
21. Cai X, Ji L, Chen Y, et al. Comparisons of weight changes between sodium-glucose cotransporter 2 inhibitors treatment and glucagon-like peptide-1 analogs treatment in type 2 diabetes patients: a meta-analysis. *J Diabetes Investig*. 2017;8(4):510-517.
22. Fonseca V, Gill J, Zhou R, Leahy J. An analysis of early insulin glargine added to metformin with or without sulfonylurea: impact on glycaemic control and hypoglycaemia. *Diabetes Obes Metab*. 2011;13(9):814-822.
23. Bolen S, Tseng E, Hutfless S, et al. *Diabetes Medications for Adults With Type 2 Diabetes: An Update.* Comparative effectiveness reviews no. 173. Rockville, MD: Agency for Healthcare Research and Quality. Report 16-EHC013-EF. https://effectivehealthcare. ahrq.gov/topics/diabetes-update-2015/research/. Published April 19, 2016. Accessed February 2, 2018.
24. Grandy S, Shaunik A, Hardy E. Effects of glucagon-like peptide-1 receptor agonists on beta-cell function in patients with type 2 diabetes. *J Diabetes Metab*. 2016;7:1-8.
25. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *JAMA*. 2016;316(3):313-324.
26. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med*. 2009;361(18):1736-1747.
27. Monnier L, Wojtusciszyn A, Colette C, Owens D. The contribution of glucose variability to asymptomatic hypoglycemia in persons with type 2 diabetes. *Diabetes Technol Ther*. 2011;13(8):813-818.
28. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35(6):1364-1379.
29. Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement—executive summary. *Endocr Pract*. 2013;19(3):536-557.
30. Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. *Diabetes Care*. 2014;37(10):2763-2773.
31. Leiter LA, Gross JL, Chow F, Miller D, Johnson S, Ahren B. Once weekly glucagon-like peptide-1 receptor agonist albiglutide vs. prandial insulin added to basal insulin in patients with type 2 diabetes mellitus: results over 52 weeks. *J Diabetes Complications*. 2017;31(8):1283-1285.
32. Raccah D, Lin J, Wang E, et al. Once-daily prandial lixisenatide versus once-daily rapid-acting insulin in patients with type 2 diabetes mellitus insufficiently controlled with basal insulin: analysis of data from five randomized, controlled trials. *J Diabetes Complications*. 2014;28(1):40-44.
33. Balena R, Hensley IE, Miller S, Barnett AH. Combination therapy with GLP-1 receptor agonists and basal insulin: a systematic review of the literature. *Diabetes Obes Metab*. 2013;15(6):485-502.
34. Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Care*. 2017;40(4):614-624.
35. Soliqua 100/33 [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2018.
36. Xultophy 100/3.6 [package insert]. Plainsboro, NJ: Novo Nordisk Inc; 2016.
37. Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: The LixiLan-O randomized trial. *Diabetes Care*. 2016;39(11):2026-2035.
38. Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. *Diabetes Care*. 2016;39(11):1972-1980.
39. Niemoeller E, Souhami E, Wu Y, Jensen KH. iGlarLixi reduces glycated hemoglobin to a greater extent than basal insulin regardless of levels at screening: post hoc analysis of LixiLan-L. *Diabetes Ther*. 2017;9(1):373-382.
40. Wysham C, Bonadonna RC, Aroda VR, et al. Consistent findings in glycaemic control, body weight and hypoglycaemia with iGlarLixi (insulin glargine/lixisenatide titratable fixed-ratio combination) vs insulin glargine across baseline HbA1c, BMI and diabetes duration categories in the LixiLan-L trial. *Diabetes Obes Metab*. 2017;19(1):1408-1415.
41. Davies MJ, Leiter LA, Guerci B, et al. Impact of baseline glycated haemoglobin, diabetes duration and body mass index on clinical outcomes in the LixiLan-O trial testing a titratable fixed-ratio combination of insulin glargine/lixisenatide (iGlarLixi) vs insulin glargine and lixisenatide monocomponents. *Diabetes Obes Metab*. 2017;19(12):1798-1804.
42. Frias JP, Domingo MP, Meneghini LF, et al. Shorter time to glycemic control with fixed-ratio combination of insulin glargine and lixisenatide compared with insulin glargine treatment alone. Presented at: American Diabetes Association 77th Scientific Session; June 9-13, 2017; San Diego, CA.
43. Frias JP, Hurst W, Newton J, et al. Impact of lixisenatide (LIXI) dose range on clinical outcomes with fixed-ratio combination (FRC) iGlarLixi in patients with T2D. Presented at: American Diabetes Association 77th Scientific Session; June 9-13, 2017; SanDiego, CA.
44. Handelsman Y, Chovanes C, Dex T, et al. Efficacy and safety of insulin glargine/lixisenatide fixed-ratio combination in elderly patients with T2D. Presented at: American Diabetes Association 76th Scientific Sessions; June 10-14, 2016; New Orleans, LA.
45. Gough SC, Bode B, Woo V, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. *Lancet Diabetes Endocrinol*. 2014;2(11):885-893.
46. Holst JJ, Buse JB, Rodbard HW, et al. IDegLira improves both fasting and postprandial glucose control as demonstrated using continuous glucose monitoring and a standardized meal test. *J Diabetes Sci Technol*. 2016;10(2):389-397.
47. Buse JB, Vilsboll T, Thurman J, et al. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). *Diabetes Care*. 2014;37(11): 2926-2933.
48. Rodbard HW, Buse JB, Woo V, et al. Benefits of combination of insulin degludec and liraglutide are independent of baseline glycated haemoglobin level and duration of type 2 diabetes. *Diabetes Obes Metab*. 2016;18(1):40-48.
49. Lingvay I, Harris S, Jaeckel E, Chandarana K, Ranthe MF, Jodar E. Insulin degludec/liraglutide (IDegLira) was effective across a range of dysglycaemia and body mass index categories in the DUAL V randomized trial. *Diabetes Obes Metab*. 2018;20(1):200-205.
50. Vilsboll T, Vora J, Jarlov H, Kvist K, Blonde L. Type 2 diabetes patients reach target glycemic control faster using ideglira than either insulin degludec or liraglutide given alone. *Clin Drug Investig*. 2016;36(4):293-303.
51. Aroda VR, Bode B, Davidson J, et al. Insulin degludec/liraglutide (IDegLira) is efficacious and safe in patients with type 2 diabetes (T2D) with normal, mild or moderate renal impairment: analyses from phase 3 trials. Presented at: American Diabetes Association 77th Scientific Session; June 9-13, 2017; San Diego, CA.
52. King AB, Philis-Tsimikas A, Kilpatrick ES, Langbakke IH, Begtrup K, Vilsboll T. A fixed ra¬tio combination of insulin degludec and liraglutide (ideglira) reduces glycemic fluctua¬tion and brings more patients with type 2 diabetes within blood glucose target ranges. *Diabetes Technol Ther*. 2017;19(4):255-264.

From Randomized Controlled Trials to the Real World: Putting Evidence into Context

Lawrence Blonde, MD, FACP, MACE; Jared A. Dendy, MD; Neil Skolnik, MD; John R. White, Jr, PA-C, PharmD

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 (HbA_{1c}) 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 (**TABLE 1**).[3-5] The primary source for these definitions is the US Food and Drug Administration's (FDA) 2017 *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.[3]

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—

Lawrence Blonde, MD, FACP, MACE, Director, Ochsner Diabetes Clinical Research Unit, Frank Riddick Diabetes Institute, Department of Endocrinology, Ochsner Medical Center, New Orleans, Louisiana

Jared A. Dendy, MD, Staff Physician, Dept of Endocrinology, Ochsner Medical Center, New Orleans, Louisiana

Neil Skolnik, MD, Professor of Family and Community Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, Associate Director, Family Medicine Residency Program, Abington Jefferson Health, Abington, Pennsylvania

John R. White, Jr, PA-C, PharmD, Chair and Professor, Department of Pharmacotherapy, Washington State University, College of Pharmacy, Spokane, Washington

DISCLOSURES

Dr. Blonde discloses that he is a speaker for AstraZeneca; Janssen Pharmaceuticals, Inc.; Novo Nordisk Inc.; and Sanofi US. He is a consultant for Intarcia Therapeutics, Inc.; Janssen Pharmaceuticals, Inc.; Merck & Co.; Novo Nordisk Inc.; and Sanofi US. He has received grant research support from AstraZeneca; Janssen Pharmaceuticals, Inc.; Lexicon Pharmaceuticals, Inc.; Merck & Co.; Novo Nordisk Inc.; and Sanofi US.

Dr. Dendy discloses being a consultant for Sanofi US.

Dr. Skolnik discloses that he is on the advisory boards for AstraZeneca; Boehringer Ingelheim GmbH; Intarcia Therapeutics, Inc.; Janssen Pharmaceuticals, Inc.; Lilly USA LLC; Sanofi US; and Teva Pharmaceuticals, Inc. He is on the speakers' bureaus for AstraZeneca and Boehringer Ingelheim GmbH; and has done contracted research for AstraZeneca, Boehringer Ingelheim GmbH; and Sanofi US.

John R. White, Jr discloses that he is on the advisory board and speakers' bureau for Sanofi US.

ACKNOWLEDGEMENT

Editorial support was provided by Gregory Scott, PharmD, RPh. The authors were responsible for all content and editorial decisions.

SUPPORT

This article is sponsored by Primary Care Education Consortium and supported by funding from Sanofi US.

TABLE 1 **Glossary of terms**[3-5]

Term	Definition
Average treatment effect	The average effect of treatment on those participants who received the treatment[5]
Effectiveness trial	Also called a pragmatic trial, measures the degree of beneficial effect under real-world clinical settings[4]
Efficacy trial	Also called an explanatory trial, determines whether an intervention produces the expected result under ideal circumstances.[4] Most randomized controlled trials are efficacy trials
Medical administrative claims data	Claims arising from a person's use of the health care system (and reimbursement of health care professionals for that care)
Observational study	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
Post-marketing surveillance	Collection, analysis, and interpretation of data or other information about a marketed device or drug
Propensity score	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 baseline[5]
Propensity score matching	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 score[5]
Prospective study	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
Randomized or traditional clinical trial	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
Real-world data	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)
Real-world evidence	Clinical evidence regarding the usage and potential benefits and/or risks of a medical product derived from analysis of real-world data
Registry	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
Retrospective analysis	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

features of RCTs involving medications are[4]:

- 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
- relatively short follow-up (weeks, months, 1 to 2 years)

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.[4] Although valuable for research and required for regulatory purposes, such a comparison might not be entirely helpful to a clinician who often is more

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.[4] 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.[4,6,8] 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

TABLE 2 Example of benefits and uses of real-world data[18]

- Estimates of effectiveness in a variety of typical practice settings
- Comparison of multiple alternative interventions (eg, older vs newer drugs) or clinical strategies to inform optimal therapy choices beyond placebo comparators
- Estimates of the evolving risk-benefit profile of a new intervention, including long-term and rare clinical benefits and harms
- Examination of clinical outcomes in a diverse study population that reflects the range and distribution of patients observed in clinical practice
- Results on a broader range of outcomes, eg, patient-reported outcomes, health-related quality of life, and symptoms, than traditionally have been collected in RCTs, ie, major morbidity and short-term mortality
- Data on resource use for the cost of health care services and economic evaluation
- Information on how a product is dosed and applied in clinical practice and on levels of compliance and adherence to therapy
- Data in situations where it is not possible to conduct an RCT
- Substantiation of data collected in more controlled settings
- Data in circumstances where there is an urgency to provide reimbursement for some therapies because it is the only therapy available and might be life-saving
- Interim evidence—in the absence of RCT data—upon which preliminary decisions can be made
- Data on the net clinical, economic, and patient-reported outcome impacts following implementation of coverage or payment policies or other health management programs

Abbreviation: RCT, randomized controlled trial.

too many patients over too long a period of time and be too expensive. Other uses and benefits of RWD are shown in **TABLE 2**.[18]

There is no universally accepted definition of RWD. In its broadest terms, RWD refers to data obtained outside of an RCT.[19] 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.[20]

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.[19,20] For example, a HbA_{1C} 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.[4] 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.[4]

There are many potential limitations to RWE trials.[18] 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.[21] The collection and analysis of RWD can be costly.[17]

Limitations among RWD sources are common as well.[9] 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.[21] 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.[20]

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.[9,22,23]

CASE EXAMPLES

Beta-blocker therapy post-myocardial infarction

An early example of how RWD can lead to practice change

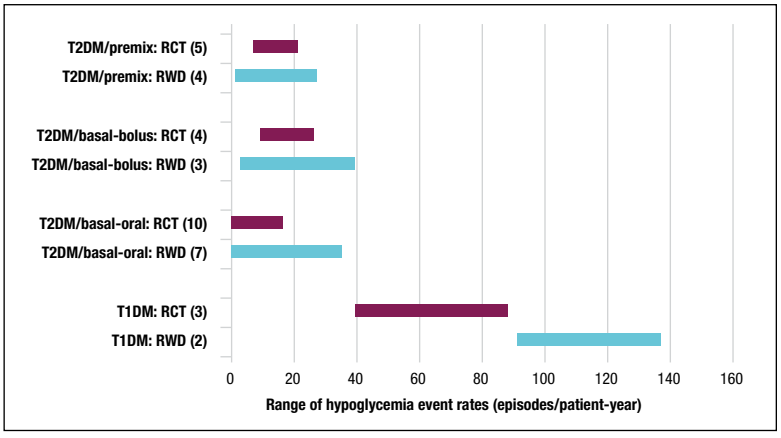
involves the use of beta-blockers in patients who had experienced a myocardial infarction (MI). In the 1990s, Medicare sponsored the Cooperative Cardiovascular Project, which analyzed medical records of >200,000 people who had experienced an MI. The analysis showed that patients who had vs those who 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).[24] 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

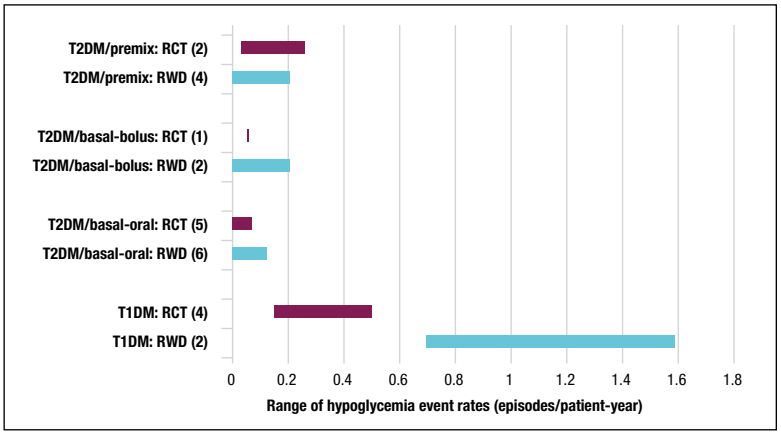
Differentiate Gla-300 clinical and Economic in reaL-world Via EMR Data study (DELIVER 2) was a retrospective analysis of the Predictive Health Intelligence Environmental database.[25] The purpose of the analysis was to evaluate clinical outcomes of patients with T2DM currently using basal insulin who 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%, HbA_{1c} 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[26]

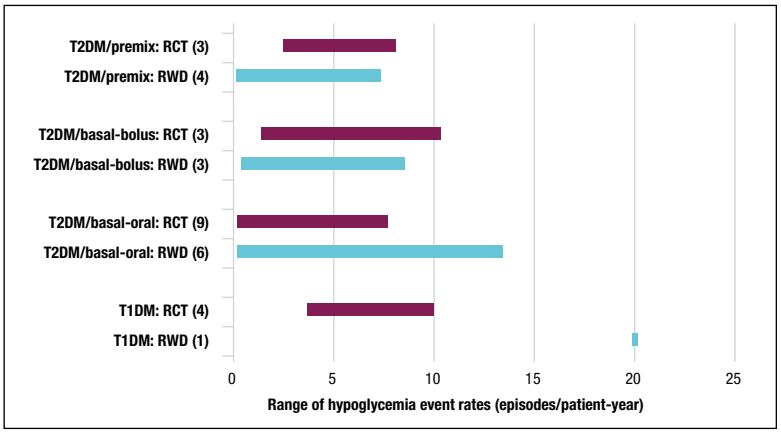
a. Nonsevere/confirmed



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.[26] 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).[26] 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

1. Pathak RD, Schroeder EB, Seaquist ER, et al. Severe hypoglycemia requiring medical intervention in a large cohort of adults with diabetes receiving care in U.S. integrated health care delivery systems: 2005-2011. *Diabetes Care.* 2016;39(3):363-370.
2. Bolen S, Tseng E, Hutfless S, et al. AHRQ comparative effectiveness reviews. In: *Diabetes medications for adults with type 2 diabetes: an update.* Rockville (MD): Agency for Healthcare Research and Quality (US); Published 2016: https://effectivehealthcare.ahrq.gov/topics/diabetes-update-2015/research. Accessed February 2, 2018.
3. US Food and Drug Administration. Use of real-world evidence to support regulatory decision-making for medical devices. Guidance for industry and Food and Drug Administration Staff. Published 2017. https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM513027.pdf. Accessed February 13, 2018.
4. Gartlehner G, Hansen RA, Nissman D, Lohr KN, Carey TS. AHRQ technical reviews. In: *Criteria for distinguishing effectiveness from efficacy trials in systematic reviews.* Rockville, MD: Agency for Healthcare Research and Quality; 2006.
5. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res.* 2011;46(3):399-424.
6. Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. *Value Health.* 2015;18(2):161-172.
7. Blumenthal D, Yu-Isenberg K, Yee J, Jena A. Real-world evidence complements randomized controlled trials in clinical decision making. *Health Affairs.* Published 2017. https://www.healthaffairs.org/do/10.1377/hblog20170927.062176/full. Accessed March 14, 2018.
8. Downing NS, Shah ND, Neiman JH, Aminawung JA, Krumholz HM, Ross JS. Participation of the elderly, women, and minorities in pivotal trials supporting 2011-2013 U.S. Food and Drug Administration approvals. *Trials.* 2016;17:199.
9. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence - what is it and what can it tell us? *N Engl J Med.* 2016;375(23):2293-2297.
10. Soule MC, Beale EE, Suarez L, et al. Understanding motivations to participate in an observational research study: why do patients enroll? *Soc Work Health Care.* 2016;55(3):231-246.
11. Geppert C, Candilis P, Baker S, Lidz C, Appelbaum P, Fletcher K. Motivations of patients with diabetes to participate in research. *AJOB Empir Bioeth.* 2014;5(4):14-21.
12. Burgess LJ, Sulzer NU, Hoosain F, Leverton N, Bliganut S, Emanuel S. Patients' motivations for participating in cardiovascular clinical trials: a local perspective. *Cardiovasc J Afr.* 2009;20(4):220-223.
13. Moorcraft SY, Marriott C, Peckitt C, et al. Patients' willingness to participate in clinical trials and their views on aspects of cancer research: results of a prospective patient survey. *Trials.* 2016;17:17.
14. Carls GS, Tuttle E, Tan RD, et al. Understanding the gap between efficacy in randomized controlled trials and effectiveness in real-world use of GLP-1 RA and DPP-4 therapies in patients with type 2 diabetes. *Diabetes Care.* 2017;40(11):1469-1478.
15. Powers JH 3rd, Patrick DL, Walton MK, et al. Clinician-reported outcome assessments of treatment benefit: report of the ISPOR Clinical Outcome Assessment Emerging Good Practices Task Force. *Value Health.* 2017;20(1):2-14.
16. Singh G, Schulthess D, Hughes N, Vannieuwenhuyse B, Kalra D. Real world big data for clinical research and drug development. *Drug Discov Today.* 2018;23(3):652-660.
17. Hubbard TE, Paradis R. Real world evidence: a new era for health care innovation. Published September 22, 2015. https://www.nehi.net/publications/66-real-world-evidence-a-new-era-for-health-care-innovation/view. Accessed February 26, 2018.
18. Garrison LP Jr, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value Health.* 2007;10(5):326-335.
19. Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Pharmacoepidemiol Drug Saf.* 2017;26(9):1033-1039.
20. Miksad RA, Abernethy AP. Harnessing the power of real-world evidence (RWE): a checklist to ensure regulatory-grade data quality. *Clin Pharmacol Ther.* 2018;103(2):202-205.
21. Hughes D, Charles J, Dawoud D, et al. Conducting economic evaluations alongside randomised trials: current methodological issues and novel approaches. *Pharmacoeconomics.* 2016;34(5):447-461.
22. US Food and Drug Administration. National Evaluation System for Health Technology (NEST). Published 2018. https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm301912.htm. Accessed April 12, 2018.
23. National Institutes of Health. NIH collaboratory living textbook of pragmatic clinical trials. Published 2018. http://www.rethinkingclinicaltrials.org. Accessed April 12, 2018.
24. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med.* 1998;339(8):489-497.
25. Zhou FL, Ye F, Berhanu P, et al. Real-world evidence concerning clinical and economic outcomes of switching to insulin glargine 300 units/mL vs other basal insulins in patients with type 2 diabetes using basal insulin. *Diabetes Obes Metab.* 2018;20(5):1293-1297.
26. Elliott L, Fidler C, Ditchfield A, Stissing T. Hypoglycemia event rates: a comparison between real-world data and randomized controlled trial populations in insulin-treated diabetes. *Diabetes Ther.* 2016;7(1):45-60.

Approaches to Increase Colorectal Cancer Screening Rates: Key Information for the Primary Care Provider

Thomas A. Mackey, PhD, APRN-BC, FAAN, FAANP

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.[1] An estimated 140,250 patients will be newly diagnosed in 2018, and 50,630 CRC-related deaths will occur.[1] 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).[2] Risk for CRC increases with age, as adults aged 65 to 74 years are most commonly diagnosed.[3] Moreover, risk increases in individuals with a family history of CRC (1.9-fold) or inflammatory bowel disease (2.9-fold).[4] Regardless of risk, screening has improved early detection rates and reduced CRC-related mortality.[5] 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.[6-8] 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.[5] 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**).[9,10] Consequently, encouraging screening for early detection of polyps and localized cancers is an important role for primary care providers.

Thomas A. Mackey, PhD, APRN-BC, FAAN, FAANP
University of Texas Health Science Center at Houston
Cizik School of Nursing
Houston, TX

DISCLOSURES
Dr. Mackey discloses being a consultant for Exact Sciences Corporation.

ACKNOWLEDGMENTS
Technical editorial assistance was provided, under the direction of the author, by Sophie Bolick, PhD, Synchrony Medical Communications, LLC, West Chester, PA.

SUPPORT
Funding for this article and support for technical assistance was provided by Exact Sciences Corporation, Madison, WI.

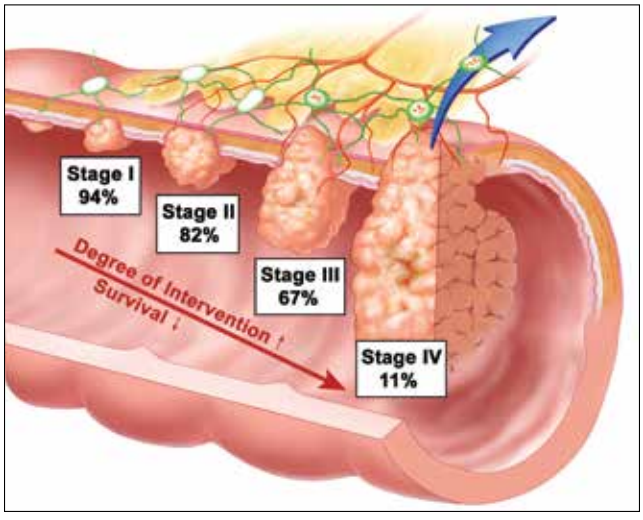
AUTHOR CONTRIBUTIONS
Dr. Mackey was involved with the concept and design of the manuscript, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and approved the final draft for submission.

COLORECTAL CANCER SCREENING

The importance of screening to detect and diagnose early-stage CRC,[11,12] as well as the favorable effect of screening on CRC-related mortality, has been established.[13] 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.[14,15] However, according to the findings of a national survey-based study, in 2012, only 65.1% of individuals 50 to 75 years of age in the United States were current with CRC screening recommendations, and 27.7% of individuals had never been screened.[16] 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; $P<.001$).[11] 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; $P<.001$).[12] 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).[17] 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).[18] 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.[19]

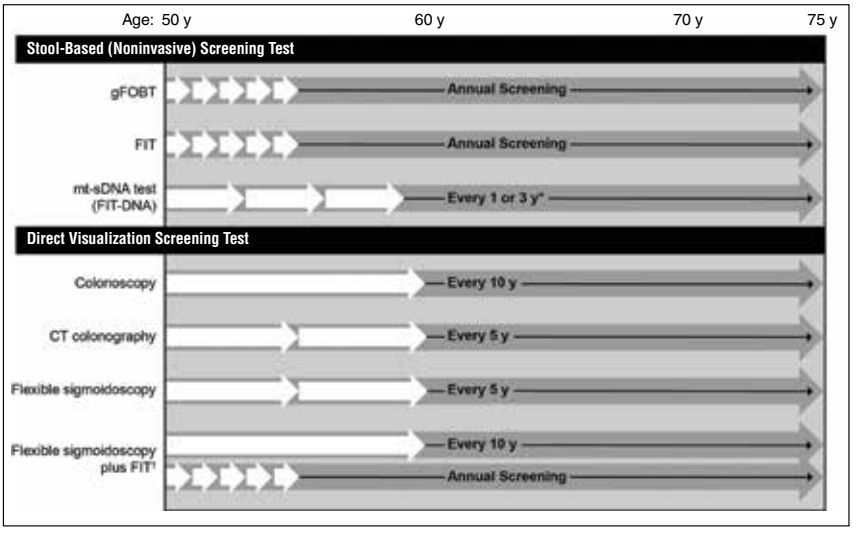
For asymptomatic adults aged 50 to 75 years at average risk for CRC, the US Preventive Services Task Force (USPSTF) and American Cancer Society (ACS) clinical practice guidelines recommend routine screening using one of a number

FIGURE 1 Colorectal cancer stages and 5-year survival rates[9,10]



Adapted from © 2005 Terese Winslow LLC

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[3,20]



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.

of stool-based and direct visualization tests (**FIGURE 2**).[3,20] The USPSTF guidelines state there is no empirical data to support one screening method over another and, therefore, do not recommend a specific modality.[3] Rather, the USPSTF considers 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.[3] Routine screening is appropriate for adults considered healthy enough to undergo treatment if CRC is detected and without comorbidities limiting life expectancy.[3] 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).[3,20] 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).[20]

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**[3,21-29]). Given detection considerations (eg, polyps and early-stage cancer may only bleed intermittently),[30] guidelines recommend stool-based testing be performed at more frequent intervals than direct visualization methods.[3,20] A positive result with any stool-based test requires follow-up diagnostic colonoscopy.[3] 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.[31] Annual screening using gFOBT, which detects the presence of the heme portion of human hemoglobulin in stool,[32,33] is convenient because 3 stool samples can be collected at home without bowel preparation prior to sample collection.[3,30] However, dietary and medication restrictions are associated with gFOBT.[34] 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).[13] The sensitivity of gFOBT for the detection of serrated (premalignant) polyps or advanced CRC was low (2.6% and 7.4%, respectively; **TABLE 2**[21,35-39]), while specificity was high (98.4% and 98.6%).[37] 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.[40] Similarly, 46.6% of individuals in

TABLE 1 Characteristics of CRC screening methods[3,21-29]

	Stool-based (noninvasive) tests			Direct visualization tests			
Parameter	**gFOBT**	**FIT**	**mt-sDNA test**	**Colonoscopy**	**CT colonography**	**Flexible sigmoidoscopy**	**Flexible sigmoid-oscopy with FIT**
Advantages	In-home testing No bowel preparation or sedation required	In-home testing No bowel preparation or sedation required Single stool sample collection No dietary or medication restrictions	In-home testing No bowel preparation or sedation required Single stool sample collection No dietary or medication restrictions Screens for altered DNA biomarkers in stool Embedded patient compliance program Greatest benefits to harms ratio (vs other modalities)	Entire colon examined by imaging Less frequent screening requirement Biopsy or polyp removal during same procedure	Less invasive vs colonoscopy Lower volumes of bowel preparation vs colonoscopy required No sedation required Lower rate of procedural complications vs colonoscopy Detection of extracolonic abnormalities	Less invasive vs colonoscopy Complete bowel preparation not required (eg, enemas) No sedation required Low rate of complications	Less invasive vs colonoscopy Encompasses both stool-based and direct visualization tests
Disadvantages	Lower sensitivity than mt-sDNA Serial stool sample collection Potential inability to detect carcinomas with little to no bleeding Requires dietary and possible drug administration restrictions prior to testing Lower specificity than FIT Positive findings require diagnostic colonoscopy	Lower sensitivity than mt-sDNA Positive findings require diagnostic colonoscopy Potential inability to detect carcinomas with little to no bleeding	Lower specificity than FIT Positive findings require diagnostic colonoscopy	Bowel preparation and sedation required Potential adverse effects related to bowel preparation, sedation, or procedure Physician skill dependent Patient time requirement (bowel preparation and test) Test performed at health care facility Patient requires transportation home after procedure	Bowel preparation required Requires insufflation* Decreased sensitivity vs colonoscopy for polyp detection Physician skill dependent Patient time requirement (bowel preparation and test) Test performed at health care facility Positive findings require diagnostic colonoscopy Radiation exposure	Restricted to distal colon (lower half) Patient time requirement (bowel preparation and test) Test performed at health care facility Positive findings require diagnostic colonoscopy	Requires 2-step completion by patient (including annual FIT) Patient time requirement (bowel preparation and test) Test performed at health care facility Positive findings require diagnostic colonoscopy
Adherence or compliance with screening†	—	Adherence FIT vs gFOBT: RR, 1.2 (95% CI: 1.03-1.3)	Compliance 88.3%	Adherence colonoscopy vs gFOBT/FIT: RR, 0.6 (95% CI, 0.4-0.8)	—	—	Adherence flexible sigmoidoscopy plus gFOBT/FIT vs gFOBT/FIT: RR, 0.6 (95% CI, 0.4-0.9)
	—			Adherence endoscopy vs stool-based tests: RR, 0.7 (95% CI: 0.6-0.8) Adherence flexible sigmoidoscopy vs stool-based tests: RR, 0.8 (95% CI: 0.6-1.04)			

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[27] or study of single screening modality (mt-sDNA).[28]

TABLE 2 Sensitivity of CRC screening methods*[21,35-39]

	Stool-based (noninvasive) tests			Direct visualization tests			
Detection parameter	**gFOBT**	**FIT**	**mt-sDNA test**	**Colonoscopy**	**CT colonography**	**Flexible sigmoidoscopy**	**Flexible sigmoidoscopy with FIT**
Any CRC	61.5%-79.4%¶	73.8%† 62.3%-83.3%¶	92.3%†	93.1%-99.5%¶	75.6%-92.4%¶	37.6%	48.6%
Advanced CRC	7.4%	22.3% 15.1%-26.3%‡	—	—	—	16.3%	31.7%
Advanced adenoma	—	23.8%† 20.8%-27%#	42.4%†	—	—	—	—
Adenoma ≥6 mm	—	—	—	92.3% 75%-93%§,¶	88.7% 73%-98%§	—	—
Adenoma ≥10 mm	17.7%-49.4%#	—	—	87.5% 89%-98%§ 93.1%-99.5%#	93.8% 67%-94%§ 75.6%-92.4%#	93.1%-95%#	—
Serrated (premalignant) polyps	2.6%	4.2%-5.2%‡	—	—	—	—	—

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.[38]

#Based on simulation models incorporating multiple screening intervals, different ages at initiation of screening, and different ages at last screening.[39]

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

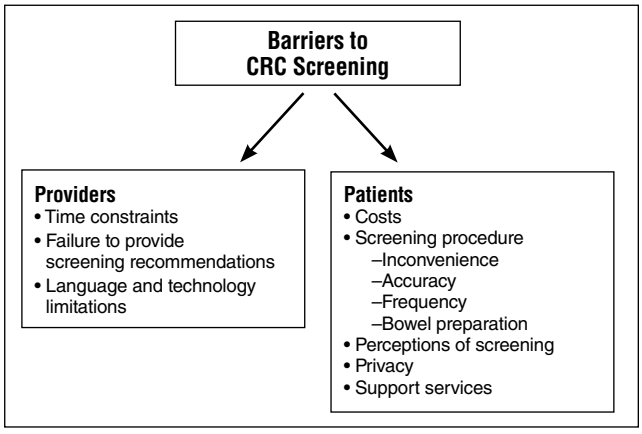
ratio of all CRC screening modalities.[3,21,46] In asymptomatic individuals at average risk for developing CRC, Imperiale et al[21] showed mt-sDNA testing had superior sensitivity for detecting CRC (any disease stage) and advanced adenomas versus FIT (CRC: 92.3% vs 73.8%, respectively, *P*=.002; advanced adenomas: 42.4% vs 23.8%, *P*<.001; **TABLE 2**).[3,21,35-39] Results from Imperiale et al demonstrated false-positive rates of 13% and 8.5% for patients aged 50 to 84 years, and 50 to 64 years, respectively.[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.[28] An initial mt-sDNA rescreening interval of 3 years is included in nationally recognized guidelines from ACS[20]; USPSTF guidelines recommend an interval of either 1 or 3 years.[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.[3] Colonoscopy allows for the visualization of the entire colon and rectum through a colonoscope.[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.[9,47] The recommended CRC screening intervals for colonoscopy and CTC are 10 years and 5 years, respectively.[3,20] Colonoscopy is the only CRC screening method in which polyps or masses can be identified and removed during the same procedure.[48-50] Individuals decline direct visualization screening methods (colonoscopy or CTC; N=151) for a variety of reasons, including time constraints (24%), the belief that screening was unnecessary due to perceived good health (23%), required bowel preparation (8%), discomfort or embarrassment (7%), and concerns regarding complications (7%).[47] A randomized, controlled study of individuals eligible for CRC screening by colonoscopy (n=5,924) or CTC (n=2,920) found significantly more declined colonoscopy compared with CTC (13% vs 7%, respectively; *P*<.001).[51] The most common reasons cited for declining screening by colonoscopy or CTC included "unpleasantness" of the screening modality (66% vs 30%, respectively; *P*<.001), inconvenience of the test preparation (34% vs 18%; *P*<.001), perception of screening as unnecessary due to lack of symptoms (23% vs 32%; *P*=.01), and time constraints (14% vs 20%; *P*=.04).[51] Colonoscopy adherence rates at 1 and 3 years have been reported to be 38.2%[52] and 38.4%[45], respectively.

In asymptomatic individuals, the sensitivity of CTC to detect adenomas ≥6 mm was 88.7%, which was lower than colonoscopy (92.3%; **TABLE 2**).[21,35-39] However, the sensitivity of CTC to detect large-sized polyps (ie, ≥10 mm) was greater than that of colonoscopy (93.8% vs 87.5%, respectively).[36] No high-quality studies have validated the sensitivity and specificity of colonoscopy. Colonoscopy and CTC are associated with operator-dependent factors that can affect the quality of the procedure and, in some cases, potentially harm the patient.[38,48] Factors associated with oversight of polyps during colonoscopy include poor bowel preparation and/or endoscopist training and experience.[48] Additional considerations specific to CTC include extracolonic findings leading to unnecessary testing and anxiety, and exposure to ionizing radiation during the procedure.[25,38,49] 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).[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).[53]

Flexible sigmoidoscopy is not commonly used as a CRC screening test in the United States.[54] Flexible sigmoidoscopy involves endoscopic examination of the distal colon following cleansing by enema[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).[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.[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.[3,56] Current USPSTF and ACS guidelines recommend screening of asymptomatic individuals in the United States every 5 years when using flexible sigmoidoscopy.[3,20] 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**).[21,35-39,57]

FIGURE 3 Potential barriers to CRC screening[28,60-67]



Abbreviation: CRC, colorectal cancer.

The digital rectal exam is not recommended for CRC screening, as testing is limited to the lower rectum.[20] Further, any stool found during a digital rectal exam should not be screened for CRC by gFOBT or FIT.[20] 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.[58] However, current ACS and USPSTF guidelines do not include mention of the Septin serum assay.[20,59]

POTENTIAL BARRIERS TO CRC SCREENING

Potential barriers to CRC screening include issues relevant to patients and providers (**FIGURE 3**).[28,60-67] 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.[68] The ACA provides individuals access to preventive care, including CRC screening, with no out-of-pocket costs.[69] 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.[70]

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).[71] 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.[70,72] 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).[68] 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.[68] Thus, elimination of patient economic barriers is one factor of importance for increasing CRC screening in some individuals.[68]

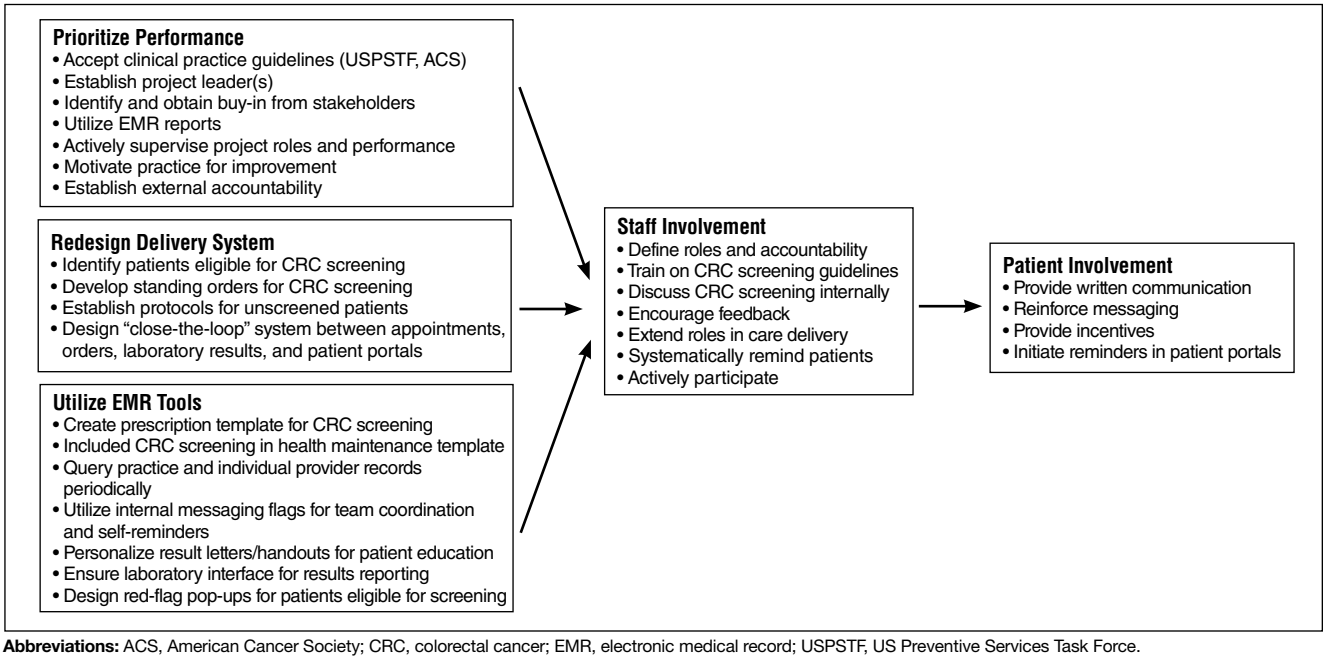
For some patients, the invasive nature of a colonoscopy presents a significant barrier. Data suggest there are 2 distinct groups: individuals who prefer colonoscopy and individuals who prefer noninvasive (stool-based) testing.[34] Another potential barrier is the role of patient perceptions, as 80.6% of 175 providers surveyed "sometimes" or "usually" encountered individuals unaware of the seriousness of CRC.[73] 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.[28,61,62]

Primary care providers play an important role in preventive screening.[74] 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).[75] 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.[67] 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.[76]

Shared decision-making regarding CRC screening methods is an important factor in adherence.[52] 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.[44] 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).[52] Barriers primary care providers may encounter in shared decision making include language[65,66] and technological limitations, as some patients lack internet access or the skills required to navigate internet-based educational tools.[66,77]

Increasing screening rates with stool-based testing may require increased patient navigation. In a study of eligible

FIGURE 4 Suggestions for improvements to CRC screening processes in primary care



Abbreviations: ACS, American Cancer Society; CRC, colorectal cancer; EMR, electronic medical record; USPSTF, US Preventive Services Task Force.

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**).[3,21-28] 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.[79,80] 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.[43]

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).[83] Further, close coordination between the primary care provider and specialist can help improve scheduling, bowel preparation, and adherence with follow-up procedures.[83] 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).[30] 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. ●

REFERENCES

1. American Cancer Society. Cancer facts & figures 2018. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2018.html. Accessed July 9, 2018.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(1):7-30.
3. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for colorectal cancer: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2016;315(23):2564-2575.
4. Johnson CM, Wei C, Ensor JE, et al. Meta-analyses of colorectal cancer risk factors. *Cancer Causes Control.* 2013;24(6):1207-1222.
5. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med.* 2012;366(8):687-696.
6. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med.* 1993;329(27):1977-1981.
7. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer.* 1975;36(6):2251-2270.
8. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell.* 1990;61(5):759-767.
9. Duarte RB, Bernardo WM, Sakai CM, et al. Computed tomography colonography versus colonoscopy for the diagnosis of colorectal cancer: a systematic review and meta-analysis. *Ther Clin Risk Manag.* 2018;14:349-360.
10. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Habbema JD, Kuipers EJ. Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. *J Natl Cancer Inst.* 2009;101(20):1412-1422.
11. Toes-Zoutendijk E, Kooyker AI, Elferink MA, et al. Stage distribution of screen-detected colorectal cancers in the Netherlands. *Gut.* 2017. 10.1136/gutjnl-2017-315111.
12. Mansouri D, McMillan DC, McIlveen E, Crighton EM, Morrison DS, Horgan PG. A comparison of tumour and host prognostic factors in screen-detected vs nonscreen-detected colorectal cancer: a contemporaneous study. *Colorectal Dis.* 2016;18(10):967-975.
13. Shaukat A, Mongin SJ, Geisser MS, et al. Long-term mortality after screening for colorectal cancer. *N Engl J Med.* 2013;369(12):1106-1114.

14. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. *CA Cancer J Clin.* 2017;67(3):177-193.
15. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer.* 2010;116(3):544-573.
16. Klabunde CN. Vital signs: colorectal cancer screening test use—United States, 2012. *MMWR Morb Mortal Wkly Rep.* 2013;62(44):881-888.
17. Brenner H, Jansen L, Ulrich A, Chang-Claude J, Hoffmeister M. Survival of patients with symptom- and screening-detected colorectal cancer. *Oncotarget.* 2016;7(28):44695-44704.
18. Hung MC, Ekwueme DU, White A, et al. Estimating health benefits and cost-savings for achieving the Healthy People 2020 objective of reducing invasive colorectal cancer. *Prev Med.* 2018;106:38-44.
19. Meester RG, Doubeni CA, Zauber AG, et al. Public health impact of achieving 80% colorectal cancer screening rates in the United States by 2018. *Cancer.* 2015;121(13):2281-2285.
20. American Cancer Society. American Cancer Society recommendations for colorectal cancer early detection. https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/acs-recommendations.html. 2018. Accessed March 7, 2018.
21. Imperiale TF, Ransohoff DF, Itzkowitz SH. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med.* 2014;371(2):187-188.
22. Burt RW, Cannon JA, David DS, et al. Colorectal cancer screening. *J Natl Compr Canc Netw.* 2013;11(12):1538-1575.
23. Franco DL, Leighton JA, Gurudu SR. Approach to incomplete colonoscopy: new techniques and technologies. *Gastroenterol Hepatol (NY).* 2017;13(8):476-483.
24. Stracci F, Zorzi M, Grazzini G. Colorectal cancer screening: tests, strategies, and perspectives. *Front Public Health.* 2014;2:210.
25. Chin M, Mendelson R, Edwards J, Foster N, Forbes G. Computed tomographic colonography: prevalence, nature, and clinical significance of extracolonic findings in a community screening program. *Am J Gastroenterol.* 2005;100(12):2771-2776.
26. Provenzale D, Jasperson K, Ahnen DJ, et al. Colorectal cancer screening, version 1.2015. *J Natl Compr Canc Netw.* 2015;13(8):959-968; quiz 968.
27. Hassan C, Giorgi Rossi P, Camilloni L, et al. Meta-analysis: adherence to colorectal cancer screening and the detection rate for advanced neoplasia, according to the type of screening test. *Aliment Pharmacol Ther.* 2012;36(10):929-940.
28. Prince M, Lester L, Chiniwala R, Berger B. Multitarget stool DNA tests increases colorectal cancer screening among previously noncompliant Medicare patients. *World J Gastroenterol.* 2017;23(3):464-471.
29. Parks P. Innovation in colorectal cancer screening—there has to be a better way. *Am J Manag Care.* 2017.1-4.
30. Singal AG, Corley DA, Kamineni A, et al. Patterns and predictors or repeat fecal immunochemical and occult blood test screening in four large health care systems in the United States. *Am J Gastroenterol.* 2018. 10.1038/s41395-018-0023-x.
31. Screening for colorectal cancer: an updated systematic review for the U.S. Preventive Services Task Force No.135. Rockville, MD: Agency for Healthcare Research and Quality; 2016.
32. Young GP, Symonds EL, Allison JE, et al. Advances in fecal occult blood tests: the FIT revolution. *Dig Dis Sci.* 2015;60(3):609-622.
33. Young GP, St John DJ, Rose IS, Blake D. Haem in the gut. Part II. Faecal excretion of haem and haem-derived porphyrins and their detection. *J Gastroenterol Hepatol.* 1990;5(2): 194-203.
34. Schroy PC, 3rd, Lal S, Glick JT, Robinson PA, Zamor P, Heeren TC. Patient preferences for colorectal cancer screening: how does stool DNA testing fare? *Am J Manag Care.* 2007;13(7):393-400.
35. Kato J, Morikawa T, Kuriyama M, et al. Combination of sigmoidoscopy and a fecal immunochemical test to detect proximal colon neoplasia. *Clin Gastroenterol Hepatol.* 2009;7(12):1341-1346.
36. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med.* 2003;349(23): 2191-2200.
37. Shapiro JA, Bobo JK, Church TR, et al. A comparison of fecal immunochemical and high-sensitivity guaiac tests for colorectal cancer screening. *Am J Gastroenterol.* 2017; 112(11):1728-1735.
38. Lin JS, Piper MA, Perdue LA, et al. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA.* 2016;315(23): 2576-2594.
39. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of benefits, burden, and harms of colorectal cancer screening strategies: modeling study for the US Preventive Services Task Force. *JAMA.* 2016;315(23):2595-2609.
40. Liang PS, Wheat CL, Abhat A, et al. Adherence to competing strategies for colorectal cancer screening over 3 years. *Am J Gastroenterol.* 2016;111(1):105-114.
41. Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. *Ann Intern Med.* 2014;160(3):171.
42. Pham R, Cross S, Fernandez B, et al. "Finding the Right FIT": Rural patient preferences for fecal immunochemical test (FIT) characteristics. *J Am Board Fam Med.* 2017;30(5): 632-644.
43. Akram A, Juang D, Bustamante R, et al. Replacing the guaiac fecal occult blood test with the fecal immunochemical test increases proportion of individuals screened in a large healthcare setting. *Clin Gastroenterol Hepatol.* 2017;15(8):1265-1270, e1261.
44. Cyhaniuk A, Coombes ME. Longitudinal adherence to colorectal cancer screening guidelines. *Am J Manag Care.* 2016;22(2):105-111.
45. Singal AG, Gupta S, Skinner CS, et al. Effect of colonoscopy outreach vs fecal immunochemical test outreach on colorectal cancer screening completion: A randomized clinical trial. *JAMA.* 2017;318(9):806-815.
46. Cologuard Physician Brochure [package insert]. Madison, WI: Exact Sciences; 2014.
47. Scott RG, Edwards JT, Fritschi L, Foster NM, Mendelson RM, Forbes GM. Community-based screening by colonoscopy or computed tomographic colonography in asymptomatic average-risk subjects. *Am J Gastroenterol.* 2004;99(6):1145-1151.
48. Bonnington SN, Rutter MD. Surveillance of colonic polyps: Are we getting it right? *World J Gastroenterol.* 2016;22(6):1925-1934.
49. Sali L, Regge D. CT colonography for population screening of colorectal cancer: hints from European trials. *Br J Radiol.* 2016;89(1068):20160517.
50. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet.* 2010;375(9726):1624-1633.
51. de Wijkerslooth TR, de Haan MC, Stoop EM, et al. Reasons for participation and nonparticipation in colorectal cancer screening: a randomized trial of colonoscopy and CT colonography. *Am J Gastroenterol.* 2012;107(12):1777-1783.
52. Inadomi JM, Vijan S, Janz NK, et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. *Arch Intern Med.* 2012;172(7):575-582.
53. Bellini D, Rengo M, De Cecco CN, Iafrate F, Hassan C, Laghi A. Perforation rate in CT colonography: a systematic review of the literature and meta-analysis. *Eur Radiol.* 2014;24(7):1487-1496.
54. American Cancer Society. Colorectal cancer screening tests. ACS 2017:1-12.
55. Yang J, Du XL, Li ST, et al. Characteristics of differently located colorectal cancers support proximal and distal classification: a population-based study of 57,847 patients. *PLoS One.* 2016;11(12):e0167540.
56. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *N Engl J Med.* 2012;366(25):2345-2357.
57. Iovanescu D, Frandes M, Lungeanu D, Burlea A, Miutescu BP, Miutescu E. Diagnosis reliability of combined flexible sigmoidoscopy and fecal-immunochemical test in colorectal neoplasia screening. *Onco Targets Ther.* 2016;9:6819-6828.
58. EpiPro Colon. Germantown, MD: EpiGenomics. 2016.
59. Bibbins-Domingo K. Colorectal cancer screening recommendations-reply. *JAMA.* 2016;316(16):1717.
60. Xu Y, Levy BT, Daly JM, Bergus GR, Dunkelberg JC. Comparison of patient preferences for fecal immunochemical test or colonoscopy using the analytic hierarchy process. *BMC Health Serv Res.* 2015;15:175.
61. Schroy PC, 3rd, Heeren TC. Patient perceptions of stool-based DNA testing for colorectal cancer screening. *Am J Prev Med.* 2005;28(2):208-214.
62. Sly JR, Edwards T, Shelton RC, Jandorf L. Identifying barriers to colonoscopy screening for nonadherent African American participants in a patient navigation intervention. *Health Educ Behav.* 2013;40(4):449-457.
63. Nagelhout E, Comarell K, Samadder NJ, Wu YP. Barriers to colorectal cancer screening in a racially diverse population served by a safety-net clinic. *J Community Health.* 2017;42(4):791-796.
64. Honein-AbouHaidar GN, Kastner M, Vuong V, et al. Systematic review and meta-study synthesis of qualitative studies evaluating facilitators and barriers to participation in colorectal cancer screening. *Cancer Epidemiol Biomarkers Prev.* 2016;25(6):907-917.
65. Diaz JA, Roberts MB, Clarke JG, Simmons EM, Goldman RE, Rakowski W. Colorectal cancer screening: language is a greater barrier for Latino men than Latino women. *J Immigr Minor Health.* 2013;15(3):472-475.
66. Garcia-Dominic O, Lengerich EJ, Wray LA, et al. Barriers to CRC screening among Latino adults in Pennsylvania: ACCN results. *Am J Health Behav.* 2012;36(2):153-167.
67. Yarnall KS, Ostbye T, Krause KM, Pollak KI, Gradison M, Michener JL. Family physicians as team leaders: "time" to share the care. *Prev Chronic Dis.* 2009;6(2):A59.
68. Fedewa SA, Goodman M, Flanders WD, et al. Elimination of cost-sharing and receipt of screening for colorectal and breast cancer. *Cancer.* 2015;121(18):3272-3280.
69. Chait N, Glied S. Promoting prevention under the Affordable Care Act. *Annu Rev Public Health.* 2018. 10.1146/annurev-publhealth-040617-013534.
70. Cooper GS, Kou TD, Schluchter MD, Dor A, Koroukian SM. Changes in receipt of cancer screening in Medicare beneficiaries following the Affordable Care Act. *J Natl Cancer Inst.* 2016;108(5).
71. Han X, Robin Yabroff K, Guy GP, Jr., Zheng Z, Jemal A. Has recommended preventive service use increased after elimination of cost-sharing as part of the Affordable Care Act in the United States? *Prev Med.* 2015;78:85-91.
72. Cooper GS, Kou TD, Dor A, Koroukian SM, Schluchter MD. Cancer preventive services, socioeconomic status, and the Affordable Care Act. *Cancer.* 2017;123(9):1585-1589.
73. Brown T, Lee JY, Park J, et al. Colorectal cancer screening at community health centers: A survey of clinicians' attitudes, practices, and perceived barriers. *Prev Med Rep.* 2015;2: 886-891.
74. Selby K, Bartlett-Esquilant G, Cornuz J. Personalized cancer screening: helping primary care rise to the challenge. *Public Health Rev.* 2018;39:4.
75. Halm EA, Beaber EF, McLerran D, et al. Association between primary care visits and colorectal cancer screening outcomes in the era of population health outreach. *J Gen Intern Med.* 2016;31(10):1190-1197.
76. Smith AA, Kepka D, Yabroff KR. Advanced practice registered nurses, physician assistants and cancer prevention and screening: a systematic review. *BMC Health Serv Res.* 2014;14:68.
77. Jimbo M, Shultz CG, Nease DE, Fetters MD, Power D, Ruffin MT, 4th. Perceived barriers and facilitators of using a Web-based interactive decision aid for colorectal cancer screening in community practice settings: findings from focus groups with primary care clinicians and medical office staff. *J Med Internet Res.* 2013;15(12):e286.
78. Coronado GD, Rivelli JS, Fuoco MJ, et al. Effect of reminding patients to complete fecal immunochemical testing: a comparative effectiveness study of automated and live approaches. *J Gen Intern Med.* 2018;33(1):72-78.
79. Klabunde CN, Lanier D, Breslau ES, et al. Improving colorectal cancer screening in primary care practice: innovative strategies and future directions. *J Gen Intern Med.* 2007;22(8):1195-1205.
80. Scheid DC, Hamm RM, Ramakrishnan K, McCarthy LH, Mold JW, Oklahoma Physicians Resource/Research Network. Improving colorectal cancer screening in family medicine: an Oklahoma Physicians Resource/Research Network (OKPRN) study. *J Am Board Fam Med.* 2013;26(5):498-507.
81. Baker AN, Parsons M, Donnelly SM, et al. Improving colon cancer screening rates in primary care: a pilot study emphasising the role of the medical assistant. *Qual Saf Health Care.* 2009;18(5):355-359.
82. Arsenault P, John L, O'Brien LM. The use of the whole primary-care team, including community health workers, to achieve success in increasing colon cancer screening rate. *Healthcare Quality.* 2016;38(2):76-83.
83. Schiff GD, Bearden T, Hunt LS, et al. Primary care collaboration to improve diagnosis and screening for colorectal cancer. *Jt Comm J Qual Patient Saf.* 2017;43(7):338-350.