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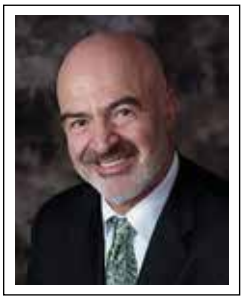

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Introduction

Innovation in medicine continues to present greater opportunities to individualize the care that we provide to our patients in the primary care setting. This seems to be especially true for patients with type 2 diabetes mellitus, where the results of cardiovascular outcome trials with newer glucose-lowering medications provide unprecedented opportunities to reduce cardiovascular risk. In the related article, the genesis and objectives of the more than 20 cardiovascular outcome trials completed to date are discussed. The results of these trials are detailed, along with their clinical implications for generally reducing cardiovascular risk in patients with type 2 diabetes mellitus, as recommended in the most recent guidelines.

New treatment options for challenging primary headache disorders continue to become available. This makes it critical that primary care providers are able to differentiate primary from secondary headaches, as well as among primary headache disorders. In the related article on cluster headache, background information on epidemiology and pathophysiology rounds out a focused discussion of the diagnostic evaluation of cluster headache in the primary care setting.

The opioid crisis has prompted a reexamination of nonprescription analgesic therapy for the treatment of patients with musculoskeletal pain. In the related article, the evidence regarding the efficacy and safety of naproxen and opioids is reviewed. A summary of several guidelines for treating various musculoskeletal conditions also is provided.

We hope that you find this *Clinician Reviews* supplement helpful in keeping you up to date and optimizing the management of your patients. As always, we welcome your comments about this special edition and suggestions for the next one.

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Efficacy and Safety of Naproxen vs Opioids for the Treatment of Musculoskeletal Pain

Stephen Brunton, MD, FAAFP; Steven M. Weisman, PhD

INTRODUCTION

Epidemiology & treatment of musculoskeletal pain

Musculoskeletal pain affects 1 in 4 adults globally and is one of the most common medical complaints in the world. Musculoskeletal pain is one of the primary reasons for self-medication and entry into the health care system,[1] while also responsible for serious long-term pain and physical disability. Musculoskeletal pains are the second most frequent cause for an individual to consult a physician, accounting for upwards of 20% of a typical primary care practice.[2] Furthermore, there are data suggesting that musculoskeletal pain is more common today than it was 40 years ago,[3] but whether this is due to heightened awareness of symptoms or increased reporting remains unclear.

Successful management of pain in the acute phase is essential to prevent transition to chronic pain.[4-6] Unfortunately, the prognosis for musculoskeletal pain is often poor, with many patients reporting continued symptoms for 6 to 12 months after first consulting with their primary care physician.[7,8] Musculoskeletal pain can also lead to unhealthy behaviors, including overeating, alcohol/drug abuse, as well as the use of more potent than needed drugs.[9-11]

Fortunately, many types of acute musculoskeletal pain can be appropriately managed and stopped from progressing into chronic conditions with both over-the-counter (OTC) and prescription analgesics. Prescription opioids are commonly used to treat musculoskeletal pain, although there is increasing awareness of the potential harm of opioid-related adverse events and misuse.[12] Importantly, most musculoskeletal aches and pains are acute in nature and self-treatable with OTC analgesics, and flares associated with chronic conditions may also be appropriate for OTC management. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat musculoskeletal pain and are among the world's most consumed prescription and OTC medications. Every day, approximately 30 million people worldwide use NSAIDs.[13] In the United States, there are an estimated 30 billion doses of NSAIDs consumed annually,[14] with over 100 million prescriptions written every year.[15] In the United States, an OTC analgesic usage rate of 76% was reported, with more women self-medicating than men.[16]

Consumers with musculoskeletal pain need a variety of options to reduce or alleviate that pain. In many cases, naproxen represents an effective, long-lasting option based on its 14-hour half-life. All day pain relief is possible with naproxen, and clinical trials demonstrate greater overall pain relief and duration of pain relief compared to acetaminophen (APAP).

The opioid crisis

Overprescribing and the availability of inexpensive street drugs have fueled a public health crisis, resulting in opioid dependence, misuse, and addiction in epidemic proportions.[17] Despite having only 4.6% of the world's population, the United States consumes 80% of the world's prescription opioids and 99% of the world's hydrocodone supply.[18] The misuse of prescription pain medication is responsible for almost half a million emergency department (ED) visits per year.[19] Greater than 75% of those visits are the result of diversion, which occurs when people are using drugs that were prescribed to another.[20] Data from the US Centers for Disease Control and Prevention indicate that in 2017 there were about 48,000 opioid overdose deaths. The number of overdose deaths involving opioids in 2017 was 6 times higher than in 1999. On average, 130 Americans die every day from an opioid overdose.

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DISCLOSURES

Stephen Brunton reports no conflicts of interest relative to this topic.

Steven M. Weisman is Head of Clinical and Regulatory Support at Innovative Science Solutions, a consultancy to the pharmaceutical industry, and has received consultancy fees from Bayer related to the topic of this manuscript.

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Broader use of nonopioid pharmacotherapy, including the appropriate use of OTC options, is critical to addressing the opioid crisis by preventing addiction resulting from valid prescriptions. Often the initial use of opioids starts through the valid treatment of a medical condition (pain) and, whether the initial medical condition is resolved or not, can lead to addiction. According to the World Health Organization analgesic ladder, APAP or NSAIDs should be used prior to weak opioids (eg, tramadol, codeine). If weak opioids are inadequate to provide effective pain relief, then strong opioids (eg, morphine, oxycodone, fentanyl) are indicated.[12] Nonetheless, it is not uncommon for physicians and dentists to prescribe opioids to treat pain conditions that could be adequately managed with nonopioid medications. For example, 6.4% to 8.0% of opioids dispensed annually by outpatient retail pharmacies in the United States are the result of prescriptions from dentists. Dentists are also the highest percentage prescribers for patients ages 10 to 19 years.[21-23]

Despite the issue of opioid-related adverse events and the fact that opioids are not indicated as a primary treatment for a majority of acute pain conditions,[24,25] they are still prescribed too often as first line treatment.[26] In fact, guidelines by the American College of Rheumatology,[27] American Academy of Family Physicians (AAFP),[28] American Academy of Orthopaedic Surgeons,[29] and Osteoarthritis Research Society International[30] all recommend NSAIDs as first-line treatment for various osteoarthritic conditions. Additionally, guidelines by AAFP[31] and the American College of Physicians and the American Pain Society[32] recommend NSAIDs as first-line treatment for the short-term treatment of low back pain. Acute musculoskeletal injury guidelines by the Orthopaedic Trauma Association recommend NSAIDs as first-line treatment,[33] and a guideline for ankle sprains by the National Athletic Trainers' Association[34] only recommends NSAIDs. Furthermore, the American Dental Association also recommends that dentists consider NSAID analgesics as the first-line therapy for acute pain management.[35]

Younger consumers are especially at risk: 80% of high school students who reported medical use of opioids prior to misuse acquired the substance from their own previous prescription,[36] signifying that even a medically necessary opioid prescription carries the risk for misuse. As OTC NSAIDs are indicated for use for 12 years and up, they are the recommended first-line therapy for this vulnerable population.

Literature search methodology

A comprehensive and broad literature search for all clinical trials comparing opioids and naproxen was conducted utilizing the National Center for Biotechnology Information and the National Library of Medicine's PubMed database. A more targeted search for randomized clinical trials comparing opioids and NSAIDs supplemented the main search. Abstracts of all search results were reviewed and the full articles reviewed for any relevant results. Citations in the relevant articles were also reviewed to ensure thoroughness.

EFFICACY OF NAPROXEN AND OPIOIDS IN TREATING MUSCULOSKELETAL PAIN

Opioids to treat musculoskeletal pain

A systematic review with meta-analysis by Megale et al[37] that included 23 randomized placebo-controlled trials in older adults (over 60 years of age) found that opioid analgesics had only small effects on decreasing pain intensity (standardized mean difference [SMD] of -0.27; 95% CI, -0.33 to -0.20) and improving function (SMD, -0.27; 95% CI, -0.36 to -0.18), which were not associated with daily dose or treatment duration. Furthermore, the authors found that the odds of adverse events with opioids were 3 times higher (odds ratio [OR], 2.94; 95% CI, 2.33-3.72), while treatment discontinuation due to adverse events had odds 4 times higher (OR, 4.04; 95% CI, 3.10-5.25) when treating patients with opioids. The authors concluded that in this older population, opioid-related risks may outweigh the benefits.

Comparative efficacy of opioids and naproxen

A comprehensive report by the Swedish Council on Health Technology determined that weak opioids reduce mild-to-moderate osteoarthritis (OA) and low back pain by approximately 40%, and are "just as effective as NSAIDs for OA pain."[38]

Fathi et al conducted a randomized clinical trial to compare the efficacy and safety of oral oxycodone with naproxen to control acute pain in adult patients with soft tissue injury (n=150). The study also evaluated whether patients needed additional doses of analgesics during the first 24 hours after discharge from the ED. The study found that pain scores were similar in the oxycodone and naproxen groups before medication (6.21±0.9 vs 6.0±1.0), 30 minutes after medication (4.5±1.4 vs 4.4±1.2), and 60 minutes after medication (2.5±1.3 vs 2.6±1.3). Twelve (16.0%) patients in the oxycodone group and 5 (6.6%) patients in the naproxen group required more analgesic during the first 24 hours after ED discharge, although this was not statistically significant. Patients in the oxycodone group experienced a statistically significant difference in adverse effects, with the most common being nausea (13.3%), vomiting (8.0%), dizziness (5.3%), drowsiness (4.0%), and pruritis (2.7%). The authors concluded that oral oxycodone is as effective as naproxen in pain control for soft tissue injury but has a less favorable safety profile.[39]

Several other studies have demonstrated hydrocodone and oxycodone to be noninferior to nonopioids in reducing

pain. One study found that neither 5 mg oxycodone/325 mg APAP nor 5 mg hydrocodone/300 mg APAP were superior to 400 mg ibuprofen/1000 mg APAP in the treatment of acute extremity pain in emergency departments.[24] Similarly, adding APAP/oxycodone to 500 mg by mouth naproxen (twice daily) for acute lower back pain did not increase efficacy when compared to naproxen alone.[40,41] Further, the use of oxycodone- or hydrocodone-APAP combination pills increases the risk of under-dosing APAP when attempting to minimize opioid dosing or, conversely, over-dosing APAP when attempting to reach a sufficient opioid effect.[42] These studies support the notion that naproxen and oxycodone/APAP have a similar magnitude of effect, yet differential degrees of adverse effects.

Naproxen to treat musculoskeletal pain

Not all NSAIDs have demonstrated equivalent efficacy in treating musculoskeletal pain. Unlike APAP, NSAIDs are potent inhibitors of prostaglandin synthesis and target the inflammatory pain encountered with acute infection, tissue injury, and surgical trauma. Therefore it is not surprising that when treating inflammatory pain, NSAIDs have consistently been shown to be more effective than APAP.[43,44]

Jevsevar et al recently conducted a network meta-analysis of data from multiple trials to determine the relative effectiveness of nonsurgical treatments for knee OA, including APAP, ibuprofen, intra-articular (IA) or joint injections of cortisone, platelet-rich plasma, hyaluronic acid, and several NSAIDs (eg, naproxen, celecoxib, and diclofenac). The analysis included 53 randomized controlled knee OA trials, requiring at least 30 participants per treatment group and durations of at least 28 days. The authors found that naproxen has the highest probability for improving function and naproxen was the only treatment showing clinical significance for improving function compared with placebo. Cumulative probabilities revealed that naproxen is also the most effective individual knee OA treatment for improving both pain and function, and when combined with IA corticosteroids, it is the most probable to improve pain and function.[45]

There are numerous guidelines for the treatment of various musculoskeletal conditions that were put forth by medical organizations and associations using publicly available literature and weighting recommendations using level of evidence. The majority of guidelines recommend the use of NSAIDs, including naproxen, for first-line treatment, often over opioids. The **TABLE** summarizes some of these guidelines.

Additionally, it should be noted that naproxen has been shown to be more cost-effective in managing joint pain than opioids, celecoxib, or the standard of care.[46] Finally, treating pain with NSAID analgesics rather than opioids helps fight the ongoing prescription opioid abuse epidemic.

SAFETY IN MUSCULOSKELETAL PAIN POPULATIONS

Safety of opioids in musculoskeletal pain populations

Opioid treatment is associated with many adverse effects, some of them serious and life-threatening. Gastrointestinal adverse effects including nausea, vomiting, cramping, and constipation are notable risks associated with chronic opioid use.[47,48] Opioid-induced constipation is sometimes refractory to treatment[49] and could, in serious cases, lead to bowel obstruction and possibly hospitalization or death.[50] Dry mouth and miosis are other common adverse reactions. Less frequent adverse effects include hypothermia, cardiovascular depression (hypotension, bradycardia), headache, urinary retention, ureteric or biliary spasm, muscle rigidity, myoclonus (with higher doses), and flushing.[51,52] Another possible adverse effect is opioid-induced hyperalgesia, which results in more pain instead of less.[53,54] Opioid neurotoxicity can result in dizziness, confusion, hallucinations, delirium, and/or sedation, leading to accidents and unintended consequences, including falls and fractures.[55] Opioids also have an effect on respiratory physiology, which may lead to unproductive ventilation and obstruction of the upper airway as a result of decreased central respiratory drive, respiratory rate, and tidal volume.[56]

A commonly cited statistic regarding the misuse of opioids is "a 1% risk of addiction."[11,57,58] This statistic comes from a single paragraph letter to the editor of The New England Journal of Medicine based on limited exposure with inpatients. There was no description of study methods.[59] Subsequent published studies have demonstrated a risk of addiction to prescription opioids of 3% to 45%, when used as part of long-term treatment. Furthermore, if prescription opioids are used beyond 12 weeks, 50% of patients will continue to use them after 5 years.[60] Other studies have verified that conversion to long-term use after 90 days increases risk of addiction.[61-64]

Zeng et al examined the association of tramadol prescription within a population of patients with OA with all-cause mortality, compared with 5 other analgesic medications, in a sequential, propensity score–matched cohort study in the United Kingdom. The patients in the cohort study had initial prescriptions of tramadol (n=44,451), naproxen (n=12,397), diclofenac (n=6,512), celecoxib (n=5,674), etoricoxib (n=2,946), or codeine (n=16,922). The authors found that during the 1-year follow-up, 278 deaths (23.5/1000 person-years) occurred in the tramadol cohort and 164 (13.8/1000 person-years) occurred in the naproxen

TABLE Guidelines for musculoskeletal pain

Condition/indication	Recommendations (Excerpted/adapted from citations, with strength/level of evidence where available)	Supporting guidelines
Arthritis	Oral NSAIDs are conditionally recommended[a] as first-line pharmacologic management of knee, hand, and hip OA.	ACR 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in OA of the Hand, Hip, and Knee[27]
	NSAIDs are superior to acetaminophen for treating moderate to severe OA (Evidence rating A[b]).	AAFP 2012: Osteoarthritis: Diagnosis and Treatment[28]
	Oral or topical NSAIDs or tramadol (Ultram) should be used in people with symptomatic knee OA (SOR: strong[c]). No recommendation can be made for or against the use of acetaminophen, opioids, or pain patches (SOR: inconclusive[c]).	AAOS 2013 Evidence-Based Guideline for Treatment of OA of the Knee (2nd Edition)[29]
	Oral nonselective NSAIDs are recommended as a first-line pharmacologic therapy for knee only OA or for multi-joint OA in people without comorbidities (Quality of evidence: good[d]).	OARSI 2014 Guidelines for the Non-Surgical Management of Knee Osteoarthritis[30]
Low back pain	NSAIDs, opioids, and topiramate (Topamax) are more effective than placebo in the short-term treatment of nonspecific chronic low back pain. (Evidence rating A[b]) There is no difference between different types of NSAIDs, and no evidence that acetaminophen is better than placebo.	AAFP 2018 Recommendations for Mechanical Low Back Pain[31]
	For patients with low back pain, clinicians should consider the use of medications with proven benefits in conjunction with back care information and self-care. Clinicians should assess severity of baseline pain and functional deficits, potential benefits, risks, and relative lack of long-term efficacy and safety data before initiating therapy (strong recommendation, moderate-quality evidence[e]). For most patients, first-line medication options are acetaminophen or NSAIDs. NSAIDs are recommended for acute (<4 weeks) and sub-acute or chronic (>4 weeks) treatment of low back pain.	American College of Physicians and American Pain Society Joint 2001 Guidelines for Low Back Pain[32]
Acute musculoskeletal injury	The panel recommends for the routine use of NSAIDs as part of a comprehensive analgesic plan for operative and nonoperative fracture care (strong recommendation, low-quality evidence[f]). Because of the potential for misuse of all opioids, the panel recommends that the prescriber should use the lowest effective dose for the shortest period possible (strong recommendation, high-quality evidence).	OTA 2019 Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury[33]
	Nonsteroidal anti-inflammatory drugs, administered orally or topically, reduce pain and swelling and improve short-term function after ankle sprains (evidence category: A).[g]	NATA 2013 Position Statement: Conservative Management and Prevention of Ankle Sprains in Athletes[34]
Dental pain	NSAIDs have been shown to be more effective at reducing pain than opioid analgesics and are therefore recommended as the first-line therapy for acute pain management.	ADA 2019 Oral Health Topics: Oral Analgesics for Acute Dental Pain[35]

Abbreviations: AAFP, American Academy of Family Physicians; AAOS, American Academy of Orthopaedic Surgeons; ACR, American College of Rheumatology; ADA, American Dental Association; NATA, National Athletic Trainers' Association; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; OTA, Orthopaedic Trauma Association.

[a] ACR Conditional recommendations mean that the majority of informed patients would choose the recommended management but many would not, so clinicians must ensure that patients' care is in keeping with their values and preferences.

[b] AAFP evidence rating A- Consistent, good-quality patient-oriented evidence

[c] AAOS Recommendations- Strong: benefits of the approach clearly exceed the potential harm, and/or the quality of the supporting evidence is high. Inconclusive: lack of compelling evidence, resulting in an unclear balance between benefits and potential harm.

[d] OARSI quality of evidence: The methodological rigor of the highest level of evidence used. Meta-analyses and systematic reviews were assigned a quality rating of "Good", "Fair", or "Poor" using the Assessment of Multiple Systematic Reviews Tool (AMSTAR). The Cochrane Risk of Bias Assessment Method was used to rate randomized clinical trials.

[e] The panel strongly recommends that clinicians consider offering the intervention to eligible patients based on benefits clearly outweighing risks.

[f] OTA recommendations and quality of evidence: The grading of the evidence was based on the study designs, number of studies, sample sizes, and consistency of results among different studies. "Strong" = practices in which benefits are sure to outweigh potential harms.

[g] NATA evidence category A: Recommendation based on consistent and good-quality patient-oriented evidence.

cohort (rate difference, 9.7 deaths/1000 person-years [95% CI, 6.3-13.2]; hazard ratio, 1.71 [95% CI, 1.41-2.07]), and mortality was also higher for tramadol compared with diclofenac, celecoxib, and etoricoxib. Compared to codeine, no statistically significant difference in all-cause mortality was observed.[65]

Safety of naproxen in musculoskeletal pain populations

The safety profile of naproxen is well characterized, and much has been written on this topic. Like all NSAIDs, naproxen presents small, but important, increased CV risk, and particularly an increased GI bleeding risk, both of which are associated with dose and duration of use. However, short-term use has not demonstrated the same safety signals. A review of the clinical pharmacology and cardiovascular safety of naproxen by Angiolillo and Weisman (2017) found that the balance of evidence indicates that the low cyclooxygenase-2 (COX-2) selectivity of naproxen results in a lower cardiovascular risk than that of other NSAIDs, as cardiovascular risk is associated with COX-2 selectivity. The authors concluded that "the over-the-counter use of naproxen is expected to pose minimal cardiovascular risk."[66]

White et al (2018) recently published a comprehensive review of the cardiorenal safety of the most commonly used NSAIDs, including naproxen, in the context of historical regulatory concerns over COX-2 selective drugs and revised labels and the completion of the PRECISION trial. The thorough review by the authors of the published literature suggests that cardiovascular risk is low when OTC formulations are used as directed by the labels. Data from randomized trials with OTC doses do demonstrate lower rates of CV events compared with higher doses used in studies examining prescription strength NSAIDs. Furthermore, the results of PRECISION demonstrate absolute cardiovascular event rates that were lower than expected with the long-term use of prescription-strength NSAIDs in a population enriched for CV disease. The authors conclude that observational data support the notion of low CV risk for NSAIDs used at OTC doses and durations.[67]

A recent publication by Kyerematen et al compared the rates of adverse events reported with nonprescription doses of naproxen, ibuprofen, APAP, and placebo in multiple dose, multi-day (7 to 10 days) clinical trials. Retrospective collection of safety data from 8 randomized, controlled trials included patients who consumed a fixed-dose regimen of 220 to 750 mg naproxen per day for 7 to 10 days (n=1494). The authors found that the safety profile of naproxen closely resembles that of placebo, with similar rates of adverse events as ibuprofen and APAP. The most frequently reported adverse events were mild-to-moderate in severity and related to the gastrointestinal system, with no differences between groups.[68]

Of course, the benefit-risk ratio of naproxen for the treatment of musculoskeletal pain should be considered at the individual patient level, with particular regard for any underlying conditions that may increase cardiovascular risk. Lastly, naproxen is nonaddictive, and therefore could help physicians and patients avoid the harm associated with opioid addiction.

CONCLUSIONS

The balance of evidence suggests that naproxen has a favorable adverse event profile compared to opioids. Naproxen can be used in many types of musculoskeletal pain besides OA and is safe for use by minors aged 12 years and up to effectively treat musculoskeletal pain, with wider safety margins and advantages over other NSAIDs and APAP. Naproxen has the most consistent and demonstrably favorable thromboembolic, and overall cardiovascular, safety profile among the most commonly used non-aspirin NSAIDs.[69-72] All pain guidelines recommend exploring and exhausting nonopioid pharmacotherapy options prior to opioid pharmacotherapy, including the use of NSAIDs such as naproxen. Lastly, even though self-medication with OTC naproxen is an effective and appropriate pain relief option for treating minor aches and pains, health care providers and patients should be properly educated regarding the benefits and risks of naproxen compared to opioids, particularly for those who are, or may be, at risk of adverse effects. ●

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Making the Diagnosis of Cluster Headache

Vince Martin, MD

DEFINITION OF CLUSTER HEADACHE

The International Classification of Headache Disorders, 3rd edition (ICHD-3) describes cluster headache (CH) as attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal, or in any combination of these sites, lasting 15 to 180 minutes and occurring from once every other day to eight times a day (Table 1).[1] The pain is associated with one or more autonomic signs or symptoms ipsilateral to the headache and the intensity is often described as excruciating. Patients are usually unable to lie down and characteristically pace the floor.[1]

CH attacks occur in series lasting for weeks or months (so-called cluster periods or bouts) and are usually separated by remission periods lasting months or years.[1] One-quarter of patients are reported to have only a single cluster period in their lifetime.[1] Attacks tend to exhibit a circadian as well as circannual pattern, that is, occur at the same time(s) each year, particularly during the spring and fall.[2-4] During a cluster period, attacks occur regularly and may be provoked by alcohol, histamine, or nitroglycerin.[1] Other possible triggers include weather changes, smells, and bright or flashing lights.[5]

CH is classified as either episodic or chronic. Episodic CH attacks occur in periods lasting from seven days to one year, although they usually last between two weeks and three months. In episodic CH, cluster periods are separated by pain-free periods lasting at least three months. Eighty-five to 90% of patients with CH meet the definition for episodic CH.[1]

In contrast, approximately 10% to 15% of patients with CH have chronic CH.[1] Chronic CH attacks occur without a remission period, or with remissions lasting <3 months, for at least one year.[1] Chronic CH may arise *de novo* or evolve from episodic CH. In some patients, chronic CH changes into episodic CH.[1]

EPIDEMIOLOGY

CH is a rare headache disorder with a lifetime prevalence of approximately 0.12%.[6] The age at first occurrence of CH is typically between 20 and 40 years, although onset has been observed earlier.[1,7,8] In addition, a second, smaller peak in the incidence of onset has been shown in later decades of life in some studies.[9,10] CH predominantly affects men with a men to women ratio of approximately 3 or 4 to 1.[1,3,6] This ratio has decreased over the past few decades for reasons that remain unclear.[4] Some evidence indicates a lower men to women ratio in cases of familial CH.[11]

RISK FACTORS

Smoking

Cigarette smoking is strongly associated with CH. A review of the medical records of 374 men with CH showed that 88.8% of patients with episodic CH had a positive smoking history, with 78.9% of patients with episodic CH being current smokers. For chronic CH, 95.1% had a positive smoking history, with 87.8% smoking at the time they developed chronic CH.[12] Findings from the US Cluster Headache Survey showed that 73% had a positive smoking history, with 51% indicating smoking at the time they developed CH.[5]

Genetics

First- and second-degree relatives of people with CH are more likely to have CH than the general population. Epidemiologic evidence indicates the risk for CH is five to 18 times higher than the general population for first-degree relatives, and one to three times higher for second-degree relatives.[13] For families in which several members have CH, the disorder can vary among them with respect to episodic or chronic presentation and the presence of autonomic symptoms.[13]

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TABLE 1. ICHD-3 diagnostic criteria for cluster headache.[1]

A. At least five attacks fulfilling criteria B-D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)[1]
C. Either or both of the following:
1. at least one of the following symptoms or signs, ipsilateral to the headache:
a) conjunctival injection and/or lacrimation
b) nasal congestion and/or rhinorrhea
c) eyelid edema
d) forehead and facial sweating
e) miosis and/or ptosis
2. a sense of restlessness or agitation
D. Occurring with a frequency between one every other day and eight per day[2]
E. Not better accounted for by another ICHD-3 diagnosis.

[Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 38(1), pp. 1-211. Copyright © 2018 by the International Headache Society. Reprinted by permission of SAGE Publications, Ltd.]

[1]During part, but less than half, of the active time-course of cluster headache, attacks may be less severe and/or of shorter or longer duration.

[2]During part, but less than half, of the active time-course of cluster headache, attacks may be less frequent.

Head trauma

Some evidence suggests there may be an association between head trauma and CH.[14] Results of the US Cluster Headache Survey showed a history of head trauma in 18% of patients who subsequently developed CH.[5] Another investigation involving retrospective review of the medical records of all men with CH referred to one headache center over a 20-year period (N=374) showed that 35.9% of patients with episodic CH and 54.7% of patients with chronic CH had a history of head trauma.[12] In more than 75% of men whose head trauma preceded CH onset, the average time interval between the two events was 10.1 years, suggesting no association between the two.[12]

PATHOPHYSIOLOGY

CH is a primary headache disorder that involves interaction of three key structures within the central nervous system. These include the trigeminovascular system, autonomic nervous system (trigeminal autonomic reflex), and hypothalamus.[2,4,15] The trigeminovascular system consists of neurons of the trigeminal nerve that innervate cerebral blood vessels and dura mater.[2] The hypothalamus appears to play a large role in CH and is activated first, followed by the trigeminovascular and autonomic nervous systems.[15]

The hypothalamus includes the circadian system thought to be responsible for the clocklike regularity of CH, as well as areas that may be responsible for the restlessness observed with CH.[15] Molecules modulated by the hypothalamus, such as melatonin, are altered in patients with CH.[15]

The trigeminovascular system is responsible for the pain observed in CH.[15] Pain input is first received through the ophthalmic branch from the forehead, eye, dura, and large cranial vessels. These inputs are projected to several nociceptive nuclei in the brainstem and upper cervical cord, then to the thalamus, and finally to the pain neuromatrix. The trigeminovascular system has several signaling molecules including calcitonin gene-related peptide and substance P, which are elevated during a CH attack.[15,16]

Areas of the autonomic system involved in CH stem from the superior salivatory nucleus to the sphenopalatine ganglion.[15] Autonomic features such as lacrimation, conjunctival injection, and other cranial autonomic features of CH involve either parasympathetic overactivation or sympathetic inactivation. Among several signaling molecules in the autonomic system, the levels of vasoactive intestinal peptide and pituitary adenylate cyclase-activating peptide are elevated during a CH attack.[15-17]

DIAGNOSIS

CASE SCENARIO

MJ is a 31-year-old man seen in the office complaining of episodes of excruciating left-sided head pain. The headaches tend to occur at night and last a couple of hours. During the headache attacks, he has tearing and redness of his left eye and is very restless/agitated.

The diagnosis of CH is primarily a clinical one based on history and detailed neurological examination.[7,18] A concomitant headache disorder may be observed since some patients with CH also experience another headache disorder.[1] Laboratory evaluation is not useful in diagnosing CH except when needed to exclude a secondary headache disorder. Magnetic resonance imaging (MRI) of the brain can be used to rule out other etiologies.[7] In patients with CH, MRI reveals significant enlargement of the anterior hypothalamic gray matter ipsilateral to the headache side compared with controls.[19] Moreover, functional MRI has demonstrated significant cerebral activation in the ipsilateral hypothalamic gray matter during an attack.[20]

Clinical features

CH attacks are unilateral, affecting the peri- and retro-orbital regions and the temple, sometimes involving the teeth

TABLE 2. Common features of cluster headache[1-4,18,21]

Typical age of onset	20-40 years
Sex ratio	M>F
Quality of pain	Stabbing, piercing, sharp, burning
Pain intensity	Severe or very severe
Localization	 Unilateral around the eye, above the eye, or near the temple
Duration of attacks	15-180 minutes
Frequency of attacks	Every one or two days up to 8 times per day
Periodicity	Attacks occur during cluster bouts; cluster bouts can follow circannual periodicity; attacks can follow circadian periodicity
Autonomic manifestations	Yes
Behavior	Restlessness, agitation
Triggers	Alcohol, histamine, nitroglycerin

(Table 2).[1-4,18,21] The pain is excruciating, often described as severe, intense, sharp, and burning, with a clear onset and resolution.[2] The pain may be compared to poking the eye with a white-hot needle or knife.[18] During an attack, patients experience one or more cranial autonomic symptoms ipsilateral to the pain, including lacrimation, eye redness, eye discomfort such as grittiness, ptosis, nasal congestion, rhinorrhea, aural fullness, throat swelling, and flushing.[2] Restlessness and agitation are prominent features during an attack and are highly sensitive and specific for CH.[2] Patients are cognitively alert, but may be irritable and aggressive.[18] Once an attack terminates, patients are usually symptom-free until their next attack.[2,18]

Attacks tend to exhibit a circadian pattern, often occurring at night during sleep.[2,3] For unknown reasons, recurrent cluster attacks or bouts also exhibit a circannual rhythm, often occurring in the spring and autumn.[4,5,18] Similar to restlessness and agitation, circadian and circannual cyclicity are not observed in all patients with CH, but when present, they are very suggestive of CH.[18]

MISDIAGNOSIS AND DIAGNOSTIC DELAY

CH is often a debilitating disorder that, during the worst attacks, causes excruciating pain.[1] Patients with CH often experience a delay in diagnosis resulting in prolonged morbidity and exposure to unnecessary diagnostic procedures and treatments. A systematic review showed that the mean time to correct diagnosis in the United States ranged from 6.6 to 8.5 years, with one study showing that 42% of patients waited more than 5 years to receive a correct diagnosis of CH.[22] A systematic literature review of US and non-US studies reported that diagnoses received prior to a CH diagnosis included a wide variety of headache and non-headache disorders.[22] In the US, the number of diagnoses received prior to CH was 3.9. In addition to various investigations to diagnose a secondary headache such as radiologic procedures, patients received a wide spectrum of pharmacologic, surgical, and alternative medicine treatments.[22]

Several factors may contribute to diagnostic delay including the nonspecific nature of many signs and symptoms. One study involving 1163 patients with CH found a diagnostic delay more likely in those with an episodic attack pattern, presence of nausea and/or vomiting during attacks, photophobia or phonophobia, nocturnal onset, and alternating attack side.[23] Another study found that lower age at onset and pain that does not reach its peak intensity within the first five minutes were significant causes of diagnostic delay.[24]

RESOURCES

The following are resources that may be helpful in diagnosing CH, as well as providing education to patients with CH.

- American Headache Society
  - Case vignette, including signs/symptoms, diagnosis, and treatment
    https://americanheadachesociety.org/wp-content/uploads/2018/05/AHSProfilesIssue4.pdf
- American Migraine Foundation
  - Epidemiology, pathophysiology, symptoms and comorbidities
    https://americanmigrainefoundation.org/resource-library/cluster-headache-and-other-medical-conditions/
  - Symptoms and treatment
    https://americanmigrainefoundation.org/resource-library/what-to-know-about-cluster-headache/
- Clusterbusters
  - Symptoms, diagnosis, terms
    https://clusterbusters.org/about-cluster-headache/

- Cluster Headache Support Group
  - Patient experience
    https://chsg.org/2011/02/14/cluster-headache-attack/
  - Coping strategies
    https://chsg.org/guides/coping-strategies/
  - Disability laws, insurance, and employment rights
    https://chsg.org/guides/disability/
- International Classification of Headache Disorders
  - Diagnostic criteria for cluster headache
    https://www.ichd-3.org/3-trigeminal-autonomic-cephalalgias/3-1-cluster-headache/
- National Headache Foundation
  - Headache diary
    https://headaches.org/wp-content/uploads/2018/08/HEADACHE-DIARY.pdf
  - Headache Impact Test
    https://headaches.org/wp-content/uploads/2018/02/HIT-6.pdf
- National Organization for Rare Disorders
  - Description, signs/symptoms, causes, comorbidities, diagnosis, treatment
    https://rarediseases.org/rare-diseases/cluster-headache/ ●

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Reducing Cardiovascular Events in Your Patients with Type 2 Diabetes Mellitus

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading this article, the clinician should be able to:

1. Describe why glycemic control alone is insufficient to prevent long-term adverse cardiovascular outcomes
2. Characterize the cardiovascular complications observed in type 2 diabetes mellitus
3. Describe the results of cardiovascular outcome trials of glucose-lowering medications for type 2 diabetes mellitus, focusing on medications shown to reduce cardiovascular events
4. Individualize glucose-lowering medication shown to reduce cardiovascular events in patients with type 2 diabetes mellitus and with or without established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of diabetes mellitus.

DISCLOSURES

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Davida Kruger discloses that she is on the advisory board for Abbott, Dexcom, Eli Lilly, Intarcia, Janssen, Merck, Novo Nordisk, and Sanofi Aventis. She is on the speakers' bureau for Abbott, AstraZeneca, BI/Lilly, Dexcom, Eli Lilly, Insulet, Janssen, Novo Nordisk, and Valeritas. Ms. Kruger performs grant and research support to the Henry Ford Health System for Abbott, Dexcom, Helmsley Foundation, Lexicon, and Novo Nordisk. She also owns stock in Dexcom.

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CASE SCENARIO

A 67-year-old woman was diagnosed with type 2 diabetes mellitus (T2DM) 7 years ago. At the time, her glycated hemoglobin (A1c) was 8.7% and body mass index (BMI) 34.6 kg/m^2. After 10 months of lifestyle management, her A1c was 8.2% and her BMI 32.8 kg/m^2. Metformin was added and titrated to 1 g twice daily. Currently, her A1c is 7.6%, BMI 33.1 kg/m^2, blood pressure 138/94 mm Hg, and low-density lipoprotein cholesterol (LDL-C) 86 mg/dL. Her estimated glomerular filtration rate is 74 mL/min/1.73 m^2 with no evidence of albuminuria. She was diagnosed with 75% obstruction of the left anterior descending coronary artery 1.5 years ago. In addition to metformin, her current medications are hydrochlorothiazide 25 mg, rosuvastatin 20 mg, both once daily, isosorbide dinitrate 20 mg three times daily, and nitroglycerin prn.

What change would you make to her treatment plan for T2DM?

CARDIOVASCULAR RISK IN TYPE 2 DIABETES MELLITUS

As shown by the Framingham Heart Study 4 decades ago, T2DM is an independent cardiovascular (CV) risk factor, conferring a greater risk of CV disease in men and women with diabetes mellitus compared with those without diabetes mellitus (relative risk [RR], 2.1 and 2.6, respectively).[1] The risk is especially high in men and women with diabetes mellitus versus without diabetes mellitus for intermittent claudication (RR, 3.6 and 5.7, respectively) and heart failure (HF) (RR, 2.1 and 4.6, respectively). In fact, peripheral arterial disease is the most common initial presentation of CV disease in persons with T2DM (hazard ratio, 2.98).[2] Generally, the risk of cardiovascular events increases with the duration of T2DM. For example, the risk of both myocardial infarction (MI) and HF in persons with T2DM for 20 or more years is approximately twice the risk compared with persons with T2DM for less than 5 years.[3]

As shown by the United Kingdom Prospective Diabetes Study, glycemic lowering reduces CV events. For every 1% reduction of the A1c, the incidence of HF is reduced 16%, MI 14%, and stroke 12%.[4] Lower extremity amputation or fatal peripheral vascular disease is reduced 43% for every 1% reduction of the A1c. These findings are an important reminder of 2 key points to consider when managing patients with T2DM. (1) A treat-to-target approach to achieve and maintain glycemic targets is important.[5] (2) Reducing the blood glucose is important, but a key treatment objective is to reduce microvascular and macrovascular disease.

Other cardiovascular risk factors

In addition to T2DM, there are other independent modifiable risk factors for CV disease, including smoking, obesity, hyperlipidemia, and hypertension. It is, therefore, critical that all major risk factors for CV disease be identified and appropriately managed. The American Diabetes Association (ADA) does not recommend routine screening for coronary heart disease in asymptomatic patients provided that identified CV risk factors are appropriately managed.[6] Screening should be considered in patients with atypical cardiac symptoms, such as unexplained dyspnea or chest discomfort, if there are signs or symptoms of associated vascular disease, or if abnormalities on the electrocardiogram are noted.[6]

In the case scenario above, further treatment of the patient's body weight, blood pressure, and elevated LDL-C is needed to achieve recommended targets and reduce CV risk.[7-9] An angiotensin converting enzyme inhibitor or angiotensin receptor blocker should be considered as a component of antihypertensive therapy and for kidney protection. Other components of comprehensive management of patients with T2DM include antiplatelet therapy, physical activity, regular examination of eyes, mouth/teeth, skin, feet, and kidney function, as well as diabetes distress and overall quality of life.

Communication about cardiovascular risk

Communicating with patients with diabetes mellitus about CV risk is important since the majority are not aware that CV disease is the leading cause of death in patients with T2DM as shown by the "For Your Sweet Heart" survey.[10] Moreover, the survey showed that half of patients with T2DM do not realize that they are at an increased risk for CV disease and related macrovascular events. Becoming aware of this association would prompt 88% to modify their diet and 81% to talk with their health care provider. At the minimum, it is suggested that discussion with the patient with T2DM about CV risk address the following 3 questions[11]:

- What is a heart attack?
- What is my risk of having a heart attack?
- How can I reduce my risk?

The discussion might include the consequences of CV disease, including not only mortality, but reduced functioning and quality of life, as well as pain. It also may be helpful to compare the patient's risk for a CV event with a person of average risk using the American College of Cardiology ASCVD Risk Estimator (https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/). Similarly, comparing the patient's A1c, blood pressure, and cholesterol with recommended targets can help the patient focus on the path to improved CV health, beginning with a shared decision making process to develop a treatment plan.

CARDIOVASCULAR OUTCOME TRIALS

US Food and Drug Administration 2008 guidance

Approximately 20 years following publication of the

TABLE Medications for type 2 diabetes mellitus showing cardiovascular benefit

Medication	CVOT(s)	Use/prevention	MACE[a]	HF benefit	Renal benefit
GLP-1 Receptor Agonists					
Albiglutide[14]	HARMONY	2°	✔		
Dulaglutide[15,16]	REWIND	1° & 2°	✔		✔
Liraglutide[17,18]	LEADER	1° & 2°	✔		✔
Semaglutide[19]	SUSTAIN 6[b]	1° & 2°	✔		✔
Sodium Glucose Cotransporter-2 Inhibitors					
Canagliflozin[20,21]	CANVAS/-R, CREDENCE	1° & 2°	✔	✔	✔
Dapagliflozin[22,23]	DECLARE-TIMI 58	1° & 2°		✔	✔
Empagliflozin[24-26]	EMPA-REG OUTCOME	2°	✔	✔	✔

Abbreviations: CVOT, cardiovascular outcome trial; HF, heart failure; MACE, major adverse cardiovascular event.

[a]Composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke

[b]Injectable route of administration

Framingham Heart Study showing an increased risk of CV disease in patients with diabetes mellitus, a meta-analysis of 42 randomized controlled trials was published suggesting that rosiglitazone increased the risk of MI in patients with T2DM.[12] Further investigation several years later allayed these concerns, but in the interim, the US Food and Drug Administration (FDA) issued a guidance in 2008 requiring industry sponsors to demonstrate in a clinical trial that a new medication for T2DM is not associated with an unacceptable increase in CV risk compared to placebo as part of standard care in patients at increased risk of a CV event.[13] The guidance applies to all medications for T2DM developed since 2008, including the dipeptidyl peptidase-4 inhibitors (DPP-4is), glucagon-like peptide-1 receptor agonists (GLP-1RAs) (except exenatide twice-daily, since it was approved prior to issuance of the FDA guidance), and sodium glucose cotransporter-2 inhibitors (SGLT-2is).

The primary endpoint of a CV outcome trial (CVOT) is the incidence of a major adverse CV event (MACE), which is a composite of CV death, nonfatal MI, and nonfatal stroke. Most CVOTs also investigate other CV events, eg, HF and kidney function. The trials should be long enough to obtain enough events and to provide data on longer-term CV risk. They should include patients with T2DM at higher risk of CV events, eg, advanced disease, advanced age, or renal impairment.

The FDA guidance specifies that a finding of noninferiority, ie, safety comparable to placebo, is demonstrated if the upper limit of the two-sided 95% confidence interval (CI) for the estimated risk ratio is less than 1.3. If noninferiority is demonstrated, further investigation to assess CV risk reduction is allowed. A risk ratio less than 1 indicates superiority, demonstrating that the new medication reduces CV risk compared to placebo as part of standard care.

Overview of cardiovascular outcome trials

One or more CVOT has been completed for all 4 DPP-4is (alogliptin, linagliptin, saxagliptin, sitagliptin), 6 GLP-1RAs (albiglutide, dulaglutide, exenatide once-weekly, liraglutide, lixisenatide, injectable and oral semaglutide), and 3 SGLT-2is (canagliflozin, dapagliflozin, empagliflozin). The VERTIS-CV trial for ertugliflozin is ongoing. Most of the trials have included patients at high risk of CV disease (1° prevention) as well as patients with established CV disease (2° prevention). All completed CVOTs have demonstrated the new medication for T2DM is noninferior to placebo as part of standard care, thereby providing reassurance that it poses no increased CV risk.

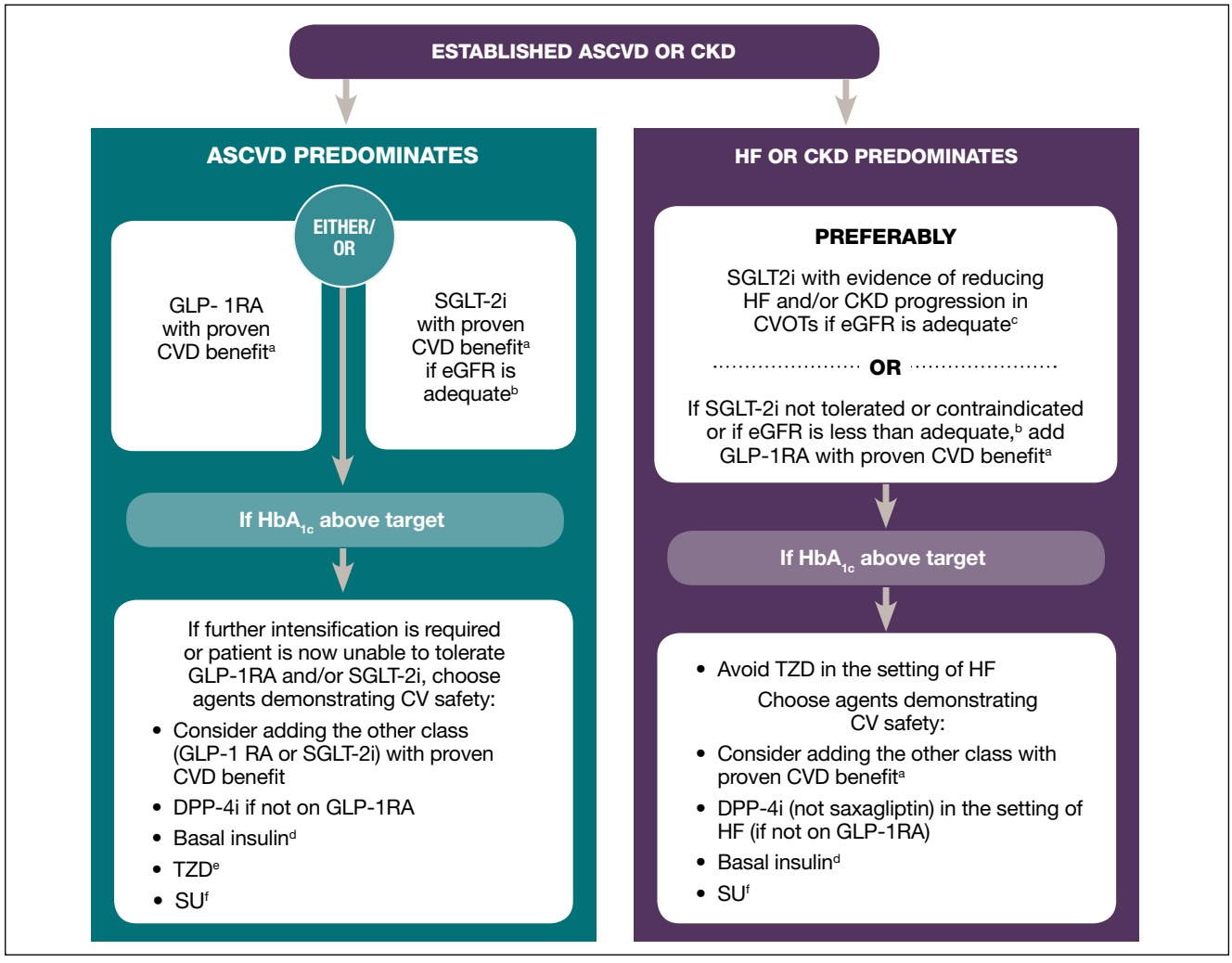
In addition, superiority, ie, significant reduction in CV risk, has been demonstrated for the primary endpoint (MACE) for the GLP-1RAs albiglutide, dulaglutide, liraglutide, and injectable semaglutide and the SGLT-2is canagliflozin and empagliflozin (**TABLE**).[14-26] Furthermore, the GLP-1RAs dulaglutide, liraglutide, and semaglutide have shown a reduction in kidney events, while empagliflozin, canagliflozin, and dapagliflozin have shown a reduction in kidney events, as well as HF events, in CVOTs.

It is also worth noting that the safety of insulin glargine U-100 has been shown to be noninferior to standard care for MACE in a head-to-head trial. [27] The safety of degludec was compared with glargine U-100 in a head-to-head trial showing degludec to be noninferior to glargine U-100 for MACE.[28] Finally, in its review of the new drug application for glargine U-300, the FDA concluded that there is no safety concern with glargine U-300 compared with glargine U-100.[29]

PATIENT-CENTRIC APPROACH TO DIABETES CARE

A key principle of the ADA Standards of Medical Care in

FIGURE Treatment of patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease or chronic kidney disease who do not achieve glycemic control with first-line therapy of metformin and comprehensive lifestyle management[31]



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcome trials; DPP-4i, dipeptidyl peptidase-4 inhibitor; FDA, US Food and Drug Administration; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; $HbA1_c$, hemoglobin A1c; HF, heart failure; SGLT-2i, sodium glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

[a] Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1RA, liraglutide is FDA approved to reduce the risk of MACE in adults with type 2 diabetes and established CVD; liraglutide and dulaglutide showed superiority for MACE outcomes in large CVOTs; semaglutide showed superiority for MACE outcomes in a safety CVOT. These results were primarily in patients with known ASCVD although there was consistent benefit in the dulaglutide trial in patients with and without established ASCVD. For SGLT-2i, evidence modestly stronger for empagliflozin > canagliflozin.

[b] Be aware that SGLT-2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use.

[c] Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and reduction in CKD progression in CV outcome trials.

[d] Degludec or glargine U-100 have demonstrated CV safety.

[e] Low dose may be better tolerated though less well studied for CVD effects.

[f] Choose later generation sulfonylurea with lower risk of hypoglycemia.

Diabetes – 2019 is for the provision of patient-centered diabetes care, ie, care that is respectful of and responsive to individual patient preferences, needs, and values, and that ensures that patient values guide all clinical decisions.[30] Medication-specific factors are an important consideration as well and include effectiveness in glycemic lowering, adverse events (particularly hypoglycemia and weight change), route of administration, cost, and contraindications/warnings.

According to the ADA, the following classes of medications are recommended for a patient *without established* atherosclerotic CV disease (ASCVD) or chronic kidney disease (CKD) who does not achieve adequate glycemic control with metformin and lifestyle management in the following situations[31]:

- Compelling need to minimize hypoglycemia: DPP-4i, GLP-1RA, SGLT-2i, thiazolidinedione
- Compelling need to minimize weight gain or promote weight loss: GLP-1RA with good efficacy for weight loss or SGLT-2i
- Cost is a major issue: sulfonylurea or thiazolidinedione

For patients *with established* ASCVD or CKD who do not achieve adequate glycemic control with metformin and lifestyle management, the ADA now provides specific recommendations for combination glucose-lowering therapy (**FIGURE,** previous page).[31] These diabetes medications do not replace the need for other therapy for ASCVD, HF, or CKD as recommended in current guidelines.

Patients where established atherosclerotic cardiovascular disease predominates

For a patient where established ASCVD predominates, the addition of either a GLP-1RA or SGLT-2i with proven CV disease benefit as reflected in FDA-approved labeling is recommended. Based on the results of the CVOTs, the FDA-approved indication for the following medications has been updated to include the following:

- Canagliflozin: to reduce the risk of MACE in adults with T2DM and established CV disease and to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with T2DM and diabetic nephropathy with albuminuria >300 mg/d[32]
- Empagliflozin: to reduce the risk of CV death in adult patients with T2DM and established CV disease[33]
- Liraglutide: to reduce the risk of MACE in adults with T2DM and established CV disease[34]

An SGLT-2i should not be initiated in a patient with an estimated glomerular filtration rate <45 mL/min/1.73 m^2. For GLP-1RAs, the strongest evidence is for liraglutide, dulaglutide, and semaglutide and for SGLT-2is, empagliflozin over canagliflozin. It should be noted that this hierarchy was determined by the ADA Standards of Care panel based on available evidence, but that the CVOTs were not head-to-head comparisons of the new medication with active treatment.

Patients where established heart failure or chronic kidney disease predominates

For a patient where HF or CKD predominates, an SGLT-2i with evidence of reducing HF and/or CKD progression is preferred provided that the eGFR is ≥45 mL/min/1.73 m^2.[31] Therefore, canagliflozin, dapagliflozin, or empagliflozin are recommended for patients with established HF or CKD.[20-26] Note that the FDA-approved indication for canagliflozin has been expanded to include a benefit in patients with CKD based upon the results of the CREDENCE trial.[21] Similarly, the FDA-approved indication for dapagliflozin has been expanded to include a benefit in patients with heart failure. If an SGLT-2i is not tolerated, the addition of a GLP-1RA with proven CV benefit is recommended. For a patient with CKD, dulaglutide, liraglutide, or semaglutide would be preferred due to their demonstrated benefits in slowing progression of kidney disease.[15,17-19]

CASE SCENARIO (SUMMARY)

This patient's inadequate glycemic control with metformin and lifestyle management indicates the need for treatment intensification. Since she has established ASCVD, the use of a GLP-1RA or SGLT-2i with proven CV benefit is recommended. Of these, the use of a medication with an approved ASCVD-related indication would be preferred, ie, canagliflozin, empagliflozin, and liraglutide.

If the patient had established HF or CKD, an SGLT-2i with proven CV benefit is recommended, ie, canagliflozin, dapagliflozin, and empagliflozin. Additional therapy to address comorbidities as recommended in current guidelines also would be necessary.

Finally, while it may be preferable to use medications approved by the FDA for reducing CV risk in patients with T2DM and established CV disease, insurance coverage may necessitate consideration of other medications in the same class. In this case, those shown to provide a CV benefit may be preferred. ●

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