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A SPECIAL SUPPLEMENT ON Hot Topics in Primary Care

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George Bakris, MD

FREE
1.0 CME CREDIT

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Brian E. Lacy, MD, PhD, FACG

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Chronic Kidney Disease in Type 2 Diabetes: Optimizing Glucose-Lowering Therapy

George Bakris, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After participating in the activity, the family physician should be able to:

- Appropriately screen for the presence of chronic kidney disease in patients with type 2 diabetes mellitus (T2DM).
- Identify chronic kidney disease at an early stage in patients with T2DM.
- Individualize evidence-based glucose-lowering therapy to slow the progression of kidney disease in patients with T2DM and 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 and kidney disease.

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Dr. Bakris discloses that he serves on the advisory boards for Boehringer Ingelheim, Janssen, Merck, Relypsa, and Vascular Dynamics. He also discloses that he has received research support from Bayer, Janssen, Novo Nordisk, and Vascular Dynamics.

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CME is available October 1, 2019 to September 30, 2020.

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

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SUPPORTER

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EPIDEMIOLOGY

Chronic kidney disease (CKD) occurs in 1 in 3 people with diabetes mellitus and 1 in 5 people with hypertension, with a prevalence of 30 million US adults (15% of the adult population).¹ Forty-five percent of new cases of end-stage kidney disease (ESKD) are due to diabetes mellitus.² While the incidence of ESKD has declined slightly over the past decade to 357 per million population in 2015,² nearly half (48%) of those with severely reduced kidney function, but

not on dialysis, are not aware of having CKD.¹ Thus, it is no surprise that CKD is a common cause of all-cause mortality and cardiovascular (CV) mortality.³ In fact, evidence suggests that CKD in people with diabetes mellitus, ie, diabetic kidney disease (DKD), may shorten a person's life span by 16 years.⁴ However, the good news is that intensive treatment to achieve a glycated hemoglobin (A1c) <6.5% and fasting total cholesterol <175 mg/dL, combined with blood pressure control to levels <140/90 mmHg and

renin-angiotensin-aldosterone system blockade, can reduce the incidence of DKD in patients with T2DM and persistent microalbuminuria at baseline.⁵ Over 7.8 years of treatment and 13.3 years of follow-up, the Steno-2 trial showed a significantly lower risk of developing DKD in intensively vs conventionally treated patients (relative risk, 0.44; 95% confidence interval [CI], 0.25 to 0.77; $P=.004$).⁵

CASE SCENARIO

A 63-year-old male is new to your practice several months ago. He reports that he had not seen a physician for many years. At the initial visit, he was diagnosed with type 2 diabetes mellitus (T2DM), hypertension, and low-density lipoprotein hypercholesterolemia. He has a family history of CKD.

- Blood pressure (BP): 148/98 mm Hg
- A1c: 8.8%
- Estimated glomerular filtration rate (eGFR): 59 mL/min/1.73 m²
- Low-density lipoprotein cholesterol (LDL-C): 146 mg/dL

Treatment was initiated with metformin 1000 mg twice daily and glimepiride 1 mg once daily since his A1c of 8.8% is $\geq 1.5\%$ above his glycemic target of $<7\%$. In addition, simvastatin 40 mg daily and lisinopril/hydrochlorothiazide 40/12.5 mg daily also were started.

6-week follow up

- BP: 136/86 mmHg
- A1c: 7.4%
- Fasting plasma glucose (FPG): 145 mg/dL
- eGFR: 62 mL/min/1.73 m²
- LDL-C: 90 mg/dL

Discussion

While the patient has had a good response to metformin and glimepiride, his A1c and FPG remain elevated (as would his postprandial glucose although not measured). As indicated in the 2019 treatment guidelines for T2DM issued by the American Diabetes Association and the American Association of Clinical Endocrinologists/American College of Endocrinology, the selection of antidiabetic medication to be added to metformin should include consideration of established atherosclerotic CV disease, heart failure, and CKD, in addition to hypoglycemia and body weight.^{6,7} It is also important to screen patients for these diseases.^{3,8,9}

SCREENING FOR CKD IN DIABETES

The identification of kidney disease in patients with T2DM requires assessing both glomerular function and urinary excretion of albumin since evaluation of either alone may

not identify all patients with kidney disease (**FIGURE**).⁶ For example, 10.1% of adults with diabetes and eGFR <60 mL/min/1.73 m² had an albumin-to-creatinine ratio (ACR) <30 mg/g in 2007-2010.¹⁰

To screen for DKD, a spot urine sample for albumin is acceptable rather than timed or 24-hour collections (**TABLE 1**),⁶ but is subject to false-negative and false-positive results. Two of three spot urine specimens collected within a 3- to 6-month period should be abnormal before considering the patient to have albuminuria.⁶ The eGFR should be calculated from the serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or some other validated formula.⁶

CASE SCENARIO (CONT'D)

The patient's eGFR of 62 mL/min/1.73 m² indicates he has evidence of kidney disease.³ However, subsequent measurement of his urinary ACR reveals a level of 200 mg/g. This coupled with his family history of kidney disease places him at moderate risk.³

Assessing the ACR is an important prognostic factor for disease progression. A recent meta-analysis involving 675,904 people (80% with diabetes mellitus) and 7462 with ESKD showed that change in ACR was consistently associated with subsequent risk of ESKD across different eGFRs, presence or absence of diabetes, and sex.¹¹ The risk for ESKD progression among those who had a sustained reduction $>30\%$ in albuminuria over 2 years was reduced by 22%. The association was somewhat stronger among patients with a higher baseline ACR than among those with a lower baseline ACR.

Screening should also seek to identify other causes of CKD since diabetes mellitus is only one of several independent risk factors for CKD. In addition to age >60 years, risk factors include uncontrolled hypertension, obesity, heart failure, tobacco use, family history, and prior history of acute kidney injury.¹²

TREATMENT

Early identification of patients with or at risk for CKD allows for early intervention with the goal of preventing progression of kidney dysfunction. Comprehensive treatment of DKD requires a combination of nonpharmacologic and pharmacologic therapy to address hyperglycemia and other risk factors for DKD. In appropriate patients, treatment includes smoking cessation and weight loss through dietary modification and increased physical activity. To alter disease progression, an angiotensin converting enzyme inhib-

FIGURE Prognosis of CKD by stage³

				Albumin-to-creatinine ratio		
				A1	A2	A3
				NL-Mildly ↑	Moderately ↑	Severely ↑
				<30 mg/g	30-300 mg/g	>300 mg/g
eGFR (mL/min/ 1.73 m ²)	G1	Normal/High	≥90	Low risk	Moderate risk	High risk
	G2	Mildly ↓	60-89	Low risk	Moderate risk	High risk
	G3a	Mildly-Moderately ↓	45-59	Moderate risk	High risk	Very high risk
	G3b	Moderately-Severely ↓	30-44	High risk	Very high risk	Very high risk
	G4	Severely ↓	15-29	Very high risk	Very high risk	Very high risk
	G5	Kidney failure	<15	Very high risk	Very high risk	Very high risk

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

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itor or angiotensin receptor blocker at maximum doses is recommended in all patients with DKD and ACR ≥30 mg/g, with the strongest evidence of benefit found in those with albuminuria >300 mg/day.^{6,13-15}

The benefits of intensive therapy vs standard therapy for glycemic control on kidney function have been well established. The United Kingdom Prospective Diabetes Study (UKPDS) showed significantly greater reduction in microalbuminuria, proteinuria, and doubling of the serum creatinine at 9 years with intensive therapy (to achieve fasting plasma glucose <108 mg/dL) vs standard therapy (primarily diet).¹⁶ The Action in Diabetes and Vascular Disease: Preterax and Diamicon Controlled Evaluation (ADVANCE) trial showed significantly greater reduction in new/worsening nephropathy, development of macroalbuminuria, and development of microalbuminuria at a median of 5 years with intensive therapy (to achieve A1c <6.5%) compared with standard therapy (to achieve A1c defined on the basis of local guidelines).¹⁷ Similarly, the Veterans Affairs Diabetes Trial (VADT) showed significantly greater reduction in worsening of albuminuria and progression from normo- to microalbuminuria/macroalbuminuria at a median of 5.6 years with intensive therapy (to achieve A1c <6.0%) compared with standard therapy (to achieve A1c defined on the basis of local guidelines).¹⁸

Cardiovascular safety of antidiabetic medications

CASE SCENARIO (CONT'D)

The patient has an A1c of 7.4% and FPG 145 mg/dL despite optimized metformin and glimepiride therapy. Based on his eGFR and ACR, he is at moderate risk of progression to ESKD. How would you modify his antidiabetic therapy?

TABLE 1 Screening recommendations for CKD in diabetes⁶

	Adults	Children/ adolescents
Who?	T1DM: Duration ≥5 years T2DM: All Comorbid hypertension: All	At puberty or age >10 years, whichever is earlier, once the child has had diabetes ≥5 years
How?	Urinary albumin (eg, spot urinary albumin-to-creatinine ratio) <i>and</i> Estimated glomerular filtration rate	Urinary albumin (morning preferred) with spot urinary albumin-to-creatinine ratio
When?	At least once a year	At least once a year

Abbreviations: CKD, chronic kidney disease; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

The choice of pharmacologic therapy for intensifying antidiabetic therapy has become more challenging in recent years due to the availability of several new classes of medications. At the same time, these options provide greater opportunity for treatment individualization.

More than a decade ago, evidence emerged suggesting an elevated risk of myocardial infarction with rosiglitazone.¹⁹ These concerns led the US Food and Drug Administration (FDA) in 2008 to require industry sponsors of new medications for T2DM to demonstrate in a clinical trial that a new medication is not associated with an unacceptable increase in CV risk relative to a control group at higher risk of a CV event.²⁰

More than 15 CV outcome trials have been completed in accordance with the FDA requirements. All completed

TABLE 2 Renal outcomes from cardiovascular outcome trials

Renal outcomes	Rate/100 patient-years		Hazard ratio (95% CI)	P	Rate/100 patient-years		Hazard ratio (95% CI)	P
	Active	Placebo			Active	Placebo		
SGLT-2 inhibitors	Canagliflozin²⁴				Dapagliflozin²⁵			
Doubling of SCr, ESKD, or renal death	0.15	0.28	0.53					
Doubling of SCr, ESKD, or renal or CV death	1.32	1.58	0.82					
Doubling of SCr and eGFR ≤ 45 mL/min/1.73 m ²								
Doubling of SCr and eGFR ≤ 45 mL/min/1.73 m ² , initiation of renal-replacement therapy, or renal death								
Initiation of renal-replacement therapy								
$\geq 40\%$ reduction in eGFR, renal-replacement therapy, or renal death	0.55	0.90	0.60 (0.47-0.77)					
$\geq 40\%$ reduction in eGFR, renal death, ESKD, or renal or CV death	1.69	2.16	0.77		1.08	1.41	0.76 (0.67-0.87)	
$\geq 40\%$ decrease in eGFR to < 60 mL/min/1.73 m ² , ESKD, or renal death					3.7	7.0	0.53 (0.43-0.66)	
Progression of albuminuria	8.94	12.87	0.73 (0.67-0.79)					
Progression to macroalbuminuria								
Incident or worsening nephropathy								
GLP-1 receptor agonists	Liraglutide^{21,22}				Semaglutide²³			
New onset of persistent macroalbuminuria or a doubling of SCr and eGFR ≤ 45 mL/min/1.73 m ² , need for continuous renal-replacement therapy, or death from renal diseases	1.5	1.9	0.78 (0.67-0.92)	0.003				
New onset of persistent macroalbuminuria	0.9	1.21	0.74 (0.60-0.91)	0.004				
New or worsening persistent macroalbuminuria, persistent doubling of SCr and eGFR < 45 mL/min/1.73 m ² , or need for continuous renal-replacement therapy					1.86	3.06	0.64 (0.46-0.88)	0.005

Abbreviations: CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GLP-1, glucagon-like peptide-1; SCr, serum creatinine; SGLT-2, sodium glucose cotransporter-2.

trials have shown the dipeptidyl peptidase-4 inhibitors (DPP-4is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), and sodium glucose cotransporter-2 inhibitors (SGLT-2is) investigated to not increase the primary composite endpoint of CV death, nonfatal myocardial infarction, and nonfatal stroke (MACE) more than 30% compared to placebo as part

of standard antidiabetic care. Moreover, some GLP-1RAs (albiglutide, dulaglutide, liraglutide, semaglutide) and SGLT-2is (canagliflozin, dapagliflozin, empagliflozin) were shown to significantly reduce the primary MACE endpoint. Furthermore, significant improvement has been observed with the GLP-1RAs liraglutide^{21,22} and semaglutide²³ and the SGLT-2is

	Rate/100 patient-years		Hazard ratio (95% CI)	P
	Active	Placebo		
Empagliflozin²⁶				
	0.63	1.15	0.54	<.001
	0.55	0.97	0.56 (0.39-0.79)	<.001
	0.63	1.15	0.54 (0.40-0.75)	<.001
	0.10	0.21	0.45 (0.21-0.97)	.04
	4.18	6.49	0.62 (0.54-0.72)	<.001
	4.78	7.60	0.61 (0.53-0.70)	<.001

It must be kept in mind that since these CV outcome trials were not head-to-head trials, comparison of results among the antidiabetic medications is not possible. However, a meta-analysis by Zelniker et al showed renal and CV benefits by all agents with different baseline levels of risk.²⁸ In addition, primary and secondary endpoints, as well as inclusion and exclusion criteria, were often different. Some trials were for primary and secondary prevention (liraglutide, semaglutide; canagliflozin, dapagliflozin), while empagliflozin was investigated only for secondary prevention. In addition, these CV outcome trials included only a small percentage of patients with pre-existing DKD.

In contrast, the CREDENCE trial included only patients with T2DM and established CKD.²⁹ Among the inclusion criteria were: age ≥ 30 years, A1c 6.5% to 12%, eGFR 30 to <90 mL/min/1.73 m², and ACR >300 to 500 mg/g. Patients were required to be stabilized on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Glucose-lowering and use of all other therapies were at the discretion of the treating physician according to local guidelines. Treatment with canagliflozin or placebo was continued until the trial was stopped by the data safety monitoring board for overwhelming efficacy to reduce CV events and slow CKD progression in the absence of a clear safety signal.

CREDENCE was stopped early at a median follow up of 2.62 years (N=4401) after a planned interim analysis showed the requisite number of primary outcome events had been reached.²⁷ From a baseline of 8.3%, the mean A1c reduction at 42 months following randomization was 0.43% with canagliflozin and 0.32% for placebo. The primary composite outcome, ie, ESKD, doubling of the serum creatinine, or renal or CV death, was significantly lower in the canagliflozin group than the placebo group (4.32 vs 6.12 per 100 patient-years, respectively; hazard ratio 0.70, 95% CI 0.59-0.82, $P=.00001$) (TABLE 3).²⁷ The number needed to treat (NNT) was 22 for the primary MACE outcome and 16 for dialysis. In addition, a significant reduction in several individual kidney endpoints were observed. Rates of adverse events and serious adverse events were similar in the canagliflozin and placebo groups, as were the rates of lower-limb amputation and fracture. The results of CREDENCE indicate that canagliflozin may be an effective treatment option for CV, as well as kidney, protection in patients with T2DM and CKD. These benefits were observed in patients with DKD, 99% of whom were on background ACE-I/ARB therapy, the only approved renoprotective medications in patients with T2DM, and in patients with eGFR well below 45 mL/min/1.73 m², the lower limit recommended for canagliflozin.

canagliflozin,²⁴ dapagliflozin,²⁵ and empagliflozin²⁶ in some kidney endpoints (TABLE 2). The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial²⁷ (discussed below), which investigated canagliflozin, is the only renal outcome trial that also had CV outcomes as prespecified secondary endpoints.

TABLE 3 Renal outcomes in patients with type 2 diabetes mellitus and established chronic kidney disease—the CREDESCENCE trial²⁷

Canagliflozin	Hazard ratio ^a (95% CI)	P
Doubling of SCr, ESKD, or renal or CV death	0.70 (0.59-0.82)	.00001
Doubling of SCr, ESKD, or renal death	0.66 (0.53-0.81)	<.001
Doubling of SCr	0.60 (0.48-0.76)	<.001
ESKD	0.68 (0.54-0.86)	.002
CV death or HF hospitalization	0.69 (0.57-0.83)	<.001
CV death, MI, or stroke	0.80 (0.67-0.95)	.01
CV death	0.78 (0.61-1.00)	.05
HF hospitalization	0.61 (0.47-0.80)	<.001

Abbreviations: CI, confidence interval; CV, cardiovascular; ESKD, end-stage kidney disease; HF, heart failure; MI, myocardial infarction; SCr, serum creatinine.

^aFavoring canagliflozin

IMPLICATIONS FOR PATIENT CARE

CKD is common in patients with T2DM and causes substantial morbidity and early death. The effectiveness of intensive antidiabetic therapy, as well as controlling other risk factors, in reducing the progression of kidney disease emphasizes the importance of early identification and intervention. Annual screening using both eGFR and ACR in patients with T2DM is, therefore, critical.

Recent data demonstrate reduced CV and renal events with several medications used for T2DM, including the GLP-1RAs liraglutide and semaglutide and the SGLT-2is canagliflozin, dapagliflozin, and empagliflozin. Only canagliflozin has been prospectively investigated in a clinical trial limited to patients with T2DM and advanced CKD, showing significant reduction in several composite and individual kidney endpoints with a very safe profile. Use of medications shown to reduce kidney events is recommended in the 2019 ADA and AACE/ACE guidelines. However, patient affordability may be a limiting factor. It is, therefore, important for healthcare providers to advocate for health care system changes that improve affordability of optimal treatment for patients. ●

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A Practical Approach to Managing Heart Failure in Type 2 Diabetes Mellitus

Javed Butler, MD; Pamela Kushner, MD

CASE SCENARIO

A 62-year-old man was diagnosed with type 2 diabetes mellitus (T2DM) three years ago (glycated hemoglobin [A1c] 8.6%). He has been treated with lifestyle management + metformin (titrated to 2 g/day) + sulfonylurea. Currently: A1c 7.4% (7.2% 6 months ago); body mass index 31.4 kg/m²; blood pressure 134/85 mmHg; estimated glomerular filtration rate 55 mL/min/1.73 m²; low-density lipoprotein cholesterol 114 mg/dL; triglycerides 320 mg/dL. He now complains of occasional shortness of breath and feeling tired.

HEART FAILURE IN DIABETES MELLITUS

The treatment of patients with T2DM has generally focused on lowering the blood glucose, specifically the A1c, to 7% or lower (or some other individualized goal).¹ This focus is based on data such as those from the Framingham Heart Study showing that DM is an independent risk factor for several cardiovascular (CV) events, including heart failure (HF).^{2,3}

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DISCLOSURES

Dr. Butler discloses that he is on the advisory board/speakers' bureaus for Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceuticals, Innolife, Janssen, Luitpold, Medtronic, Merck, Novartis, Relypsa, Stealth Peptides, scPharmaceuticals, Vifor, and ZS Pharma.

Dr. Kushner discloses that she is on the advisory board for AstraZeneca, Abbott, GlaxoSmithKline, and Janssen. She also serves on the speakers' bureaus for AstraZeneca, GlaxoSmithKline, and Janssen.

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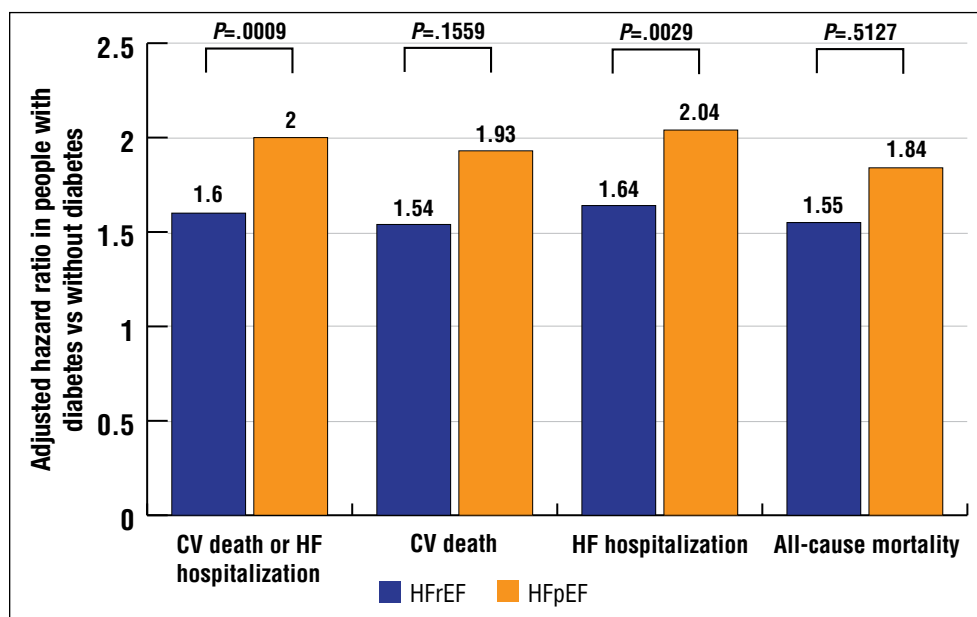
In fact, for every 1% increase in the A1c above 7.5%, there is a 15% increase in the risk of HF.⁴ Moreover, the United Kingdom Prospective Diabetes Study showed that a 1% decrease in A1c results in a significantly reduced risk of microvascular and other CV complications such as HF (-16%), myocardial infarction (MI) (-14%), and stroke (-12%).⁵ These data make it clear that, while lowering the blood glucose level is important, lowering CV risk is also a key treatment goal in people with T2DM.^{1,6}

When it comes to reducing CV events, the focus has typically been on MI and stroke, yet, in people with T2DM, HF is the most common CV complication.^{7,8} People with T2DM have more than twice the risk of HF than individuals without T2DM,^{3,9,10} and up to 40% of people with HF have DM.^{9,11-14} The risk of death in people with DM has been shown to be nearly 9 times higher for those with HF compared to those without HF.¹⁵ Risk factors for HF and DM overlap and include obesity, hypertension, sleep apnea, advanced age, dyslipidemia, anemia, coronary heart disease, and chronic kidney disease.¹⁶

HF is a common initial presentation of CV disease in T2DM, yet is undiagnosed in one-quarter of people with T2DM.

Not surprisingly, HF in people with T2DM often results in hospitalization,¹⁷ with increasing mortality with repeated hospitalization.¹⁸ Of people hospitalized for acute HF, those with DM have a worse outcome (composite of all-cause mortality, heart transplantation, and left ventricular assist device implantation) than those without DM.¹⁹ In people with HF with preserved ejection fraction (HFpEF), ie, ejection fraction >40% (also called diastolic HF²⁰), people with DM have significantly worse exercise capacity than those without DM.²¹ Moreover, in people with DM vs without DM, those with HFpEF have a significantly higher risk of CV death or HF hospitalization compared with those with HF with reduced ejection fraction (HFrEF), ie, ejection fraction ≤40% (also called systolic HF²⁰) (FIGURE).²²

FIGURE Cardiovascular outcomes in people with type 2 diabetes mellitus and heart failure with preserved ejection fraction vs heart failure with reduced ejection fraction (HFpEF vs HFrEF)²²



Abbreviations: CV, cardiovascular; HF, heart failure.

Among people with HFpEF, those with vs without DM have a more severe disease phenotype, more extensive comorbidities (obesity, hypertension, renal dysfunction, pulmonary disease, vascular disease), greater left ventricular hypertrophy, and higher circulating markers of vasoconstriction, oxidative stress, inflammation, and fibrosis.

INITIAL EVALUATION

Patients who present with dyspnea, fatigue, fluid retention, or other signs or symptoms suggesting HF should initially be evaluated by a thorough history and physical examination to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF.²⁰ Initial diagnostic testing should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, blood glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone. B-type natriuretic peptide (BNP) or N-terminal proBNP is useful. In addition to a 12-lead electrocardiogram, a chest X-ray should be done to assess heart size and pulmonary congestion and to rule out other dis-

eases that may be the cause of the patient's symptoms. A 2-dimensional echocardiogram with Doppler is the most useful diagnostic test and should be performed to assess ventricular function, size, wall thickness, wall motion, and valve function. Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients with known coronary artery disease and no angina.

FDA 2008 GUIDANCE

In 2008, the US Food and Drug Administration (FDA) issued its guidance *Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, which

required pharmaceutical sponsors to demonstrate that a new antihyperglycemic therapy for T2DM is not associated with an unacceptable increase in CV risk compared to placebo as part of standard care.²³ The guidance established requirements for assessing CV risk by conducting a randomized, double-blind, parallel, placebo-controlled, multicenter clinical trial. The trial is to assess CV risk using a composite of CV death, nonfatal MI, and nonfatal stroke, so-called major adverse CV events (MACE).

CARDIOVASCULAR OUTCOME TRIALS

The 2008 FDA guidance applies to all new antidiabetic therapies to treat T2DM and thus, includes dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), glucagon-like peptide-1 receptor agonists (GLP-1R agonists) except exenatide twice-daily, and sodium glucose cotransporter-2 inhibitors (SGLT-2 inhibitors).

Cardiovascular safety

CV outcome trials conducted in accord with the FDA guidance have been completed for 13 medications (TABLE 1).²⁴⁻³⁶ The CV outcome trial for ertugliflozin is ongoing.³⁷ All trials involved people with established CV disease (2° prevention), while some also included patients at high CV risk (1° prevention). These and other differences in study design and patient population preclude direct comparison of these trials. All

TABLE 1 Cardiovascular outcome trials of antidiabetic medications for type 2 diabetes mellitus

	CV outcome trial(s)	Use/prevention	CV safety*	CV benefit
Dipeptidyl peptidase-4 inhibitors				
Alogliptin ²⁴	EXAMINE	2°	✓	
Linagliptin ²⁵	CARMELINA	1° & 2°	✓	
Saxagliptin ²⁶	SAVOR-TIMI 53	1° & 2°	✓	
Sitagliptin ²⁷	TECOS	1° & 2°	✓	
Glucagon-like peptide-1 receptor agonists				
Albiglutide ²⁸	HARMONY	2°	✓	✓
Dulaglutide ²⁹	REWIND	1° & 2°	✓	✓
Exenatide once-weekly ³⁰	EXSCEL	1° & 2°	✓	
Liraglutide ³¹	LEADER	1° & 2°	✓	✓
Lixisenatide ³²	ELIXA	2°	✓	
Semaglutide ³³	SUSTAIN 6	1° & 2°	✓	✓
Sodium glucose cotransporter-2 inhibitors				
Canagliflozin ³⁴	CANVAS, CANVAS-R, CREDENCE	1° & 2°	✓	✓
Dapagliflozin ³⁵	DECLARE-TIMI 58	1° & 2°	✓	✓
Empagliflozin ³⁶	EMPA-REG OUTCOME	2°	✓	✓
Ertugliflozin	VERTIS CV	2°	NC	

Abbreviations: CV, cardiovascular; MI, myocardial infarction; NC, not completed.

*Non-inferior to placebo as part of standard care for the composite endpoint of CV death, non-fatal MI, and non-fatal stroke.

1°, primary prevention (ie, person who has not suffered a cardiac event) 2°, secondary prevention (ie, person who has suffered a cardiac event).

have provided reassurance that the specific DPP-4 inhibitors, GLP-1R agonists, and SGLT-2 inhibitors investigated cause no increased risk in CV safety compared to placebo as part of standard care.²⁴⁻³⁶

Cardiovascular benefit

The FDA guidance also provided standards whereby an antidiabetic medication could demonstrate superiority to placebo as part of standard care. Some of the antidiabetic medications have demonstrated superiority to placebo, thereby reducing CV risk (**TABLE 1**).^{28,29,31,33-36} These are the GLP-1R agonists albiglutide, dulaglutide, liraglutide, and semaglutide, and the SGLT-2 inhibitors canagliflozin, dapagliflozin, and empagliflozin. These results have contributed to updated recommendations in the 2019 American Diabetes Standards of Care and the 2019 American Association of Clinical Endocrinologists/American College of Endocrinology type 2 diabetes algorithm, as well as in the 2019 American College of Cardiology/American Heart Association primary prevention of CV disease guideline, to consider the use of antidiabetic medications with a CV benefit in appropriate patients earlier in the treatment algorithm.^{1,6,38} Such patients include those with established atherosclerotic CV

disease, HF, or chronic kidney disease.¹ Differences among these medications with respect to their effects on CV events provide an opportunity to go beyond reducing CV risk to also selecting individualized therapy based on patient medical history, such as HF.

Hospitalization for heart failure

Of the 13 medications that have completed a CV outcome trial, empagliflozin has been reported to significantly reduce HF hospitalization (0.94 vs 1.45 events/100 patient-years; hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.50-0.85; $P=.002$) (**TABLE 2**).^{28,29,31,33-36} In EMPA-REG OUTCOME, the significant reduction in HF hospitalization with empagliflozin was independent of history of prior MI and/or stroke and did not differ between women and men.³⁹⁻⁴¹

Other SGLT-2 inhibitors also reduce HF hospitalization. In the DECLARE-TIMI 58 trial comparing dapagliflozin with placebo, dapagliflozin significantly reduced the composite endpoint of CV death or HF hospitalization (HR, 0.83; 95% CI, 0.73-0.95; $P=.005$).³⁵ This reduction was due to a lower rate of HF hospitalization in the dapagliflozin group (HR, 0.73; 95% CI, 0.61-0.88) as there was no difference between the groups in the rate of CV death (HR, 0.98; 95% CI, 0.82-

TABLE 2 Effect on heart failure hospitalization of antidiabetic medications for type 2 diabetes mellitus shown to reduce cardiovascular risk

	Rate of heart failure hospitalization/ 100 patient-years		Hazard ratio (95% CI)	P
	Active	Placebo		
Glucagon-like peptide-1 receptor agonists				
Albiglutide ²⁸	NR	NR	NR	NR
Dulaglutide ^{a,29}	0.83	0.89	0.93 (0.77-1.12)	.46
Liraglutide ³¹	1.2	1.4	0.87 (0.73-1.05)	.14
Semaglutide ³³	1.76	1.61	1.11 (0.77-1.61)	.57
Sodium glucose cotransporter-2 inhibitors				
Canagliflozin ⁴³	0.55	0.87	0.67 (0.52-0.87)	.02
Dapagliflozin ³⁵	0.62	0.85	0.73 (0.61-0.88)	NR
Empagliflozin ³⁶	0.94	1.45	0.65 (0.50-0.85)	.002

Abbreviations: CI, confidence intervals; NR, not reported.

^aHeart failure hospitalization or urgent visit.

1.17). The significant reduction in the composite of CV death or HF hospitalization with dapagliflozin was consistent across several subgroups, including patients with established atherosclerotic CV disease, as well as history of HF at baseline.³⁵ Additional analysis showed that dapagliflozin reduced HF hospitalization both in those with and in those without HFrEF, whereas it reduced CV death only in those with HFrEF but not in those without HFrEF.⁴² With respect to canagliflozin, combined analysis of CANVAS and CANVAS-R showed a similar benefit in the MACE endpoint for patients with HFrEF and HFpEF. Canagliflozin significantly lowered the risk of HF hospitalization (HR, 0.67; 95% CI, 0.52-0.87).^{34,43} The reduction in HF hospitalization with canagliflozin vs placebo was significantly greater in those with a history of HF (HR 0.51, 95% CI 0.33-0.78), but not in those with no history of HF (HR, 0.79; 95% CI, 0.57-1.09).⁴³ Further analysis of the CANVAS program showed that canagliflozin also significantly reduced the composite of fatal HF or HF hospitalization (HR, 0.70; 95% CI, 0.55-0.89).⁴³

Results of the LEADER and SUSTAIN-6 trials showed liraglutide and semaglutide, respectively, did not significantly reduce the rate of HF hospitalization compared with placebo (**TABLE 2**).^{31,33}

The effects of the DPP-4 inhibitor saxagliptin on HF hospitalization are also notable. Results of the SAVOR-TIMI 53

trial showed that saxagliptin was associated with a significant increase in HF hospitalization vs placebo (HR, 1.27; 95% CI, 1.07-1.51; $P=.007$).²⁶

OTHER HEART FAILURE TRIALS

Other investigations outside of the CV outcome trials required by the FDA have been conducted in patients with or without DM and with or at risk of HF, many focusing on HF biomarkers. Regarding SGLT-2 inhibitors, a prospective, multicenter, open-label trial involving 58 patients with T2DM showed significant reduction in mitral inflow E and mitral e' annular velocities, indicating improved diastolic function, following 6 months of treatment with dapagliflozin.⁴⁴ Other evidence suggesting improved cardiac function with dapagliflozin includes significant reductions in the left atrial volume index and left ventricular mass index, as well as a significant reduction in B-type natriuretic peptide in patients whose level was ≥ 100 pg/mL at baseline. With respect to canagliflozin, another trial showed that it delays the rise in N-terminal-proB-type natriuretic peptide and high-sensitivity troponin I in 666 older adults with T2DM over 2 years.⁴⁵

The HF effects of the GLP-1R agonists albiglutide and liraglutide have been investigated in randomized, placebo-controlled trials. Albiglutide provided no detectable effect on cardiac function or myocardial glucose use, although there

was a modest increase in peak oxygen consumption over 12 weeks in patients with stable HF_{rEF}.⁴⁶

Several trials involving liraglutide have been conducted, providing conflicting results. One trial involving 32 patients with T2DM and New York Heart Association class II/III HF or left ventricular ejection fraction (LVEF) $\leq 45\%$ showed significant improvement in LVEF and other measures of cardiac function in patients treated with liraglutide for 52 weeks.⁴⁷ In contrast, another trial involving 241 patients (30% with T2DM, 60% with ischemic heart disease) with stable chronic HF (LVEF $\leq 45\%$) on optimal HF treatment showed liraglutide had no effect on left ventricular systolic function.⁴⁸ Moreover, liraglutide was associated with serious cardiac events (notably atrial fibrillation, ventricular tachycardia, and acute coronary syndrome) in 10% of patients. These events were not assessed in the CV outcome trial for liraglutide and merit further investigation. Another trial of patients (N=300) with or without DM recently hospitalized with HF showed the use of liraglutide for 6 months following discharge resulted in a similar percentage of patients who experienced death or HF rehospitalization as placebo.⁴⁹ In addition, the changes from baseline in LVEF, as well as left ventricular end-diastolic and -systolic volume index were similar in the 2 groups.

IMPLICATIONS FOR PRIMARY CARE

Reducing CV risk is the key treatment objective for patients with DM. To reduce the risk of HF in patients with T2DM, several steps can be taken: (1) early recognition of HF and people at increased risk of HF; (2) optimize glycemic control;

and (3) utilize and optimize medications shown to reduce HF risk, including selected medications for T2DM.

Available evidence from CV outcome trials shows that 13 of the 15 DPP-4 inhibitors, GLP-1R agonists, and SGLT-2 inhibitors currently available do not pose an increased risk of major adverse cardiovascular events. Moreover, 4 of the GLP-1R agonists (albiglutide, dulaglutide, liraglutide, semaglutide) and 3 of the SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) are superior to placebo and significantly reduce CV risk. Of these seven medications, canagliflozin, dapagliflozin, and empagliflozin significantly reduce the occurrence of HF hospitalization. Albiglutide, liraglutide, and semaglutide provide no detectable benefit on measures of HF. Beyond individualizing treatment based on factors such as hypoglycemia and body weight, impact on CV events is now an important consideration.

CASE SCENARIO (CONT'D)

Following complete evaluation, the 62-year-old male patient was diagnosed with HF_{pEF}. In addition to starting guideline-recommended therapy for HF_{pEF} (diuretic, angiotensin receptor blocker),²⁰ the decision is made to discontinue the sulfonylurea (due to increasing A1c and frequent hypoglycemia) and replace with a medication shown to reduce HF hospitalization. The American Diabetes Association prefers the use of an SGLT-2 inhibitor with evidence of reducing HF, noting that empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF-related events in a CV outcome trial.¹ If an SGLT-2 inhibitor is not tolerated or is contraindicated, a GLP-1R agonist with proven CV benefit is recommended.¹ ●

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Diabetes Management Update: Individualizing Treatment

Timothy Reid, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading this article, primary care providers will be able to:

- Summarize differences among glucagon-like peptide-1 receptor agonists and sodium glucose cotransporter-2 inhibitors regarding cardiovascular safety and benefits
- Initiate patient-centric pharmacotherapy in patients with type 2 diabetes mellitus and established cardiovascular disease who are inadequately controlled with metformin-based therapy consistent with current recommendations
- Implement simple strategies in clinical practice to address common unmet needs and concerns of patients with type 2 diabetes mellitus that impact treatment adherence and self-management

TARGET AUDIENCE

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

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CASE SCENARIO

April is a 69-year-old African American woman diagnosed with type 2 diabetes mellitus (T2DM) 11 years ago. Initial treatment with lifestyle intervention and metformin reduced her glycated hemoglobin (A1c) from 8.4% to 6.9% and her body mass index (BMI) from 32.6 kg/m² to 27.9 kg/m², which she was able to maintain for approximately 5 years. Her A1c remained at approximately 7% during this time, but began to rise as her BMI increased. Inten-

sified lifestyle intervention resulted in no further weight loss; her BMI stabilized at 33.8 kg/m². Pharmacotherapy was intensified to lower and maintain her A1c at 7.1% to 7.3% over the next several years. Over the past 3 years, her A1c has again increased and is now 7.9%. April experiences frequent symptomatic hypoglycemia, which has required treatment at the local emergency department twice in the past 4 years. April also experiences occasional symptoms of angina, which combined with her T2DM, obesity,

hypertension, and dyslipidemia, has contributed to declining treatment adherence.

April is being seen by her primary care provider following hospital discharge for a cardiovascular event. Current medications: metformin 1000 mg twice daily, pioglitazone 45 mg once daily, sitagliptin 100 mg once daily, enalapril/hydrochlorothiazide 20 mg/50 mg once daily, atorvastatin 40 mg once daily, and low-dose aspirin.

What modifications would you make to her diabetes treatment plan? Does her history of cardiovascular disease impact treatment?

CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES MELLITUS

Cardiovascular (CV) disease is common in the United States, with approximately 11% of US adults having been diagnosed with heart disease and nearly 3% with stroke.¹ Type 2 diabetes mellitus is an independent risk factor for CV disease, conferring about a two-fold excess risk for CV disease.² Moreover, in 2016, high fasting plasma glucose was among the top 5 risk factors contributing to disability-adjusted life-years in the United States.³

Peripheral arterial disease is the most common initial presentation of CV disease in patients with T2DM, followed by stroke and coronary heart disease.⁴ Beyond vascular events, persons with diabetes mellitus (DM) are at high risk for heart failure (HF) and HF-related death, as well as chronic kidney disease (CKD). People with T2DM have more than twice the risk of HF than those without T2DM,⁵⁻⁸ while up to 40% of people with HF have diabetes.^{4,7,9-13} There is a linear relationship between glycemic control and the incidence of HF with a risk ratio for HF of approximately 1.2 for each 1% increase in the A1c.^{14,15} Patients with T2DM and HF have a worse prognosis than those with T2DM without HF.¹⁶ The risk of death in persons with DM has been shown to be nearly 9 times higher for those with vs without HF.¹⁷ Of individuals hospitalized for acute HF, those with vs without DM have a worse outcome (composite of all-cause mortality, heart transplantation, and left ventricular assist device implantation).¹⁸ HF hospitalization is also more common in patients with T2DM.¹⁹

CKD also is common in patients with DM as approximately 1 in 3 US adults with DM is thought to have CKD.^{20,21} Nearly half (45%) of new cases of end-stage renal disease in the United States are due to DM.²² While the prevalence of stages 3-4 CKD has remained stable over the past decade or so,^{23,24} the increasing prevalence of DM in the United States has been followed by a proportional increase in the prevalence of diabetic kidney disease (DKD).²⁵ Moreover, the

prevalence of adults with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² and albumin-to-creatinine ratio <30 mg/g nearly tripled from 1988-1994 to 2007-2010.²⁶ This was associated with a 50% increase in the mortality rate.²⁶ In 2015, 124,000 people in the United States started treatment for end-stage renal disease²² and approximately 325 persons began treatment for kidney failure every day.^{20,22}

THE CHANGING PARADIGM OF TYPE 2 DIABETES MANAGEMENT

Over the past decade, there have been 2 important shifts in the management of patients with T2DM as reflected in treatment guidelines such as those developed by the American Diabetes Association. The first is a focus on the importance of individualizing glycemic treatment.^{27,28} This shift in focus results from the availability of several new classes of medications for T2DM with different mechanisms of glucose-lowering and very good safety profiles, particularly low incidences of hypoglycemia and weight neutrality or weight loss effects.²⁹ There has also been improved recognition that T2DM is a largely self-managed disease that is impacted by the patient's willingness and ability to adhere to the treatment plan.^{28,30,31} To better understand these issues, a collaborative relationship between patient and provider has become essential (see below).³²

The other shift has been a heightened concern about the CV safety of medications for T2DM following publication of several clinical trials and a meta-analysis related to the thiazolidinediones in 2005 to 2007. Results of the clinical trials indicated an increased risk for heart failure with rosiglitazone³³ and pioglitazone.^{34,35} The subsequent meta-analysis of 42 clinical trials demonstrated rosiglitazone was associated with a significant increase in the risk for myocardial infarction (MI) (odds ratio [OR], 1.43; 95% confidence interval [CI], 1.03-1.98; *P*=.03) and a nonsignificant increase in the risk for CV death (OR, 1.64; 95% CI, 0.98-2.74; *P*=.06).³⁶ Shortly after, the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial found no significant increase in the risk for MI with rosiglitazone, but confirmed a significant increase in risk for HF.^{37,38}

CARDIOVASCULAR OUTCOME TRIALS

Regulatory requirements

In 2008, prior to publication of the final RECORD results in 2009, the US Food and Drug Administration (FDA) took steps to assure the safety of medications for T2DM. This included issuing a guidance requiring industry sponsors to conduct a clinical trial demonstrating that a new medication for T2DM is not associated with an unacceptable increase in CV risk compared to placebo as part of standard care.³⁹ The guid-

ance applies to the dipeptidyl peptidase-4 inhibitor (DPP-4i), glucagon-like peptide-1 receptor agonist (GLP-1RA) (except exenatide twice-daily), and sodium glucose cotransporter-2 inhibitor (SGLT-2i) classes of medications.

Key recommendations in the FDA guidance included (1) assessment of major adverse CV events (MACE), a composite of CV death, nonfatal MI, and nonfatal stroke; (2) enrollment of patients with T2DM at higher risk of CV events, eg, those with advanced CV disease, advanced age, or renal impairment; and (3) study duration of at least 2 years to allow assessment of longer-term risks.³⁹

The guidance also identified that for initial FDA approval, a finding of no increase in CV risk compared to placebo as part of standard care is observed if the upper limit of the two-sided 95% confidence interval (CI) for the estimated risk ratio for MACE is less than 1.8. If the upper limit for the estimated risk ratio is found to be between 1.3 and 1.8 and the overall risk-benefit analysis is favorable, the medication is generally approved. However, a postmarketing trial is usually required to clearly demonstrate that the upper limit of the two-sided 95% CI for the estimated risk ratio is less than 1.3, in which case, a definitive finding of noninferiority regarding the CV safety of the new medication compared to placebo as part of standard care is reached. Put differently, the medication for T2DM is found to pose no increase in CV risk compared to placebo as part of standard care.

If noninferiority is demonstrated, a finding of superiority can be investigated. A finding of superiority is reached if the two-sided 95% CI for the estimated risk ratio is less than 1.0. Should this be the case, the new medication for T2DM is determined to significantly reduce CV risk compared to placebo as part of standard care and, therefore, offer a CV benefit. Medications offering a CV benefit have the potential to change the treatment paradigm for T2DM, as will be discussed below.

Results

Nearly all of the CV outcome trials required by the FDA for new medications for T2DM have been completed; note that the CV outcome trial for ertugliflozin is ongoing. Most trials have been for both primary and secondary prevention. All completed CV outcome trials have demonstrated that each new medication for T2DM poses no increased CV risk compared to placebo as part of standard care, thereby providing reassurance about the CV safety of DPP-4is, GLP-1RAs, and SGLT-2is. It is also worth noting that the CV safety of insulin glargine U-100 and insulin degludec have been assessed in clinical trials and shown to pose no increase in CV risk compared to standard care.^{40,41} In addition, the FDA judged there to be no safety concern regarding CV risk for glargine U-300 compared to glargine U-100.⁴²

In addition to CV safety, the CV outcome trials of the DPP-4is, GLP-1RAs, and SGLT-2is showed that some of these medications provide a CV benefit, ie, reduce the risk for MACE (the composite of CV death, nonfatal MI, and nonfatal stroke) compared to placebo as part of standard care. These include the GLP-1RAs albiglutide,^{43,44} dulaglutide,⁴⁵ liraglutide,^{46,47} and semaglutide,⁴⁸ and the SGLT-2is canagliflozin,^{49,50} dapagliflozin,^{51,52} and empagliflozin^{53,54} (TABLE).

The results of these trials provide an opportunity to include consideration of CV risk reduction when selecting medications for T2DM. Moreover, differences among the GLP-1RAs and SGLT-2is with respect to their effects on CV events, eg, MI, stroke, HF, and renal outcomes, provide an opportunity to further individualize therapy as recommended in the 2019 ADA Standards of Medical Care (FIGURE).²⁸

CASE SCENARIO

The rise in April's A1c to 7.9% despite treatment with optimized metformin, pioglitazone, and sitagliptin indicates the need to modify her diabetes treatment plan. Sitagliptin should be discontinued since there is no CV, HF, or CKD reduction benefit. Pioglitazone might be continued if April has established atherosclerotic cardiovascular disease (ASCVD) since there is a potential benefit, but should not be continued if April has HF or renal impairment due to fluid retention.⁵⁵ Since she has experienced a CV event, selecting a medication shown to lower CV risk is recommended.²⁸

If April had experienced a MI or stroke, a GLP-1RA is preferred with the strongest evidence for liraglutide, dulaglutide, and semaglutide. Alternatively, an SGLT-2i can be considered, with the strongest evidence for empagliflozin > canagliflozin.

If April had experienced acute heart failure or had CKD, an SGLT-2i shown to reduce HF or CKD (empagliflozin, canagliflozin, dapagliflozin) is preferred. Alternatively, a GLP-1RA (liraglutide, dulaglutide, and semaglutide) can be considered if SGLT-2i therapy is not tolerated or contraindicated or if the eGFR is below the recommended threshold for SGLT-2i therapy.

In selecting therapy, other general factors to consider include hypoglycemia, weight effects, and patient affordability. In addition, prior to initiating a GLP-1RA, a history of pancreatitis, multiple endocrine neoplasia type 2, thyroid cancer, as well as the ability to tolerate transient nausea are to be considered. Prior to initiating an SGLT-2i, the patient's eGFR must be determined and treatment not initiated if the eGFR is <45 mL/min/1.73 m² (canagliflozin, dapagliflozin, empagliflozin) or if the eGFR is 30 to <60 mL/min/1.73 m² (ertugliflozin). A comprehensive foot examination should be performed with emphasis on peripheral vascular disease and a history of amputations. Other factors to consider related to SGLT-2i therapy are the risk of urinary tract infection, genital mycotic infection, and volume depletion with all

TABLE Effects on key endpoints of medications shown to offer a cardiovascular benefit vs placebo

	Hazard ratio ^a (95% CI)					
	MACE ^b	CV death	Nonfatal MI	Nonfatal stroke	Heart failure hospitalization	Renal
Glucagon-like peptide-1 receptor agonists						
Albiglutide	0.78 (0.68-0.90)	0.93 (0.73-1.19)				
Dulaglutide	0.88 (0.79-0.99) <i>P</i> =.026			0.76 (0.61-0.95) <i>P</i> =.017		0.85 ^c (0.77-0.93) <i>P</i> =.0004
Liraglutide	0.87 (0.78-0.97) <i>P</i> =.01	0.78 (0.66-0.93) <i>P</i> =.007	0.88 (0.75-1.03) <i>P</i> =.11	0.89 (0.72-1.11) <i>P</i> =.30	0.87 (0.73-1.05) <i>P</i> =.14	0.78 ^d (0.67-0.92) <i>P</i> =.003
Semaglutide	0.74 (0.58-0.95) <i>P</i> =.02	0.98 (0.65-1.48) <i>P</i> =.92	0.74 (0.51-1.08) <i>P</i> =.12	0.61 (0.38-0.99) <i>P</i> =.04	1.11 (0.77-1.61) <i>P</i> =.57	0.64 ^e (0.46-0.88) <i>P</i> =.005
Sodium glucose cotransporter-2 inhibitors						
Canagliflozin	0.86 (0.75-0.97) <i>P</i> =.02	0.87 (0.72-1.06)	0.85 (0.69-1.05)	0.90 (0.71-1.15)	0.67 (0.52-0.87)	0.60 ^f (0.47-0.77)
Dapagliflozin	0.93 (0.84-1.03) <i>P</i> =.17	0.98 (0.82-1.17)			0.73 (0.61-0.88)	0.53 ^g (0.43-0.66)
Empagliflozin	0.86 (0.74-0.99) <i>P</i> =.04	0.62 (0.49-0.77) <i>P</i> <.001	0.87 (0.70-1.09) <i>P</i> =.22	1.24 (0.92-1.67) <i>P</i> =.16	0.65 (0.50-0.85) <i>P</i> =.002	0.54 ^h (0.40-0.75) <i>P</i> <.001

Abbreviations: CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; MI, myocardial infarction.

^aHazard ratio of active medication vs placebo.

^bMACE is a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke.

^cNew macroalbuminuria, sustained decline in eGFR \geq 30% or chronic renal replacement therapy.

^dNephropathy defined as new onset of macroalbuminuria or a doubling of the serum creatinine and an eGFR \leq 45 mL/min/1.73 m², the need for continuous renal-replacement therapy, or death from renal disease.

^eNew or worsening nephropathy including persistent macroalbuminuria, persistent doubling of the serum creatinine and an eGFR $<$ 45 mL/min/1.73 m², or the need for continuous renal-replacement therapy.

^f \geq 40% reduction in eGFR, renal-replacement therapy, or renal death.

^g \geq 40% decrease in eGFR to $<$ 60 mL/min/1.73 m², end-stage renal disease, or death from renal cause.

^hDoubling of serum creatinine accompanied by eGFR \leq 45 mL/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease.

Boxes shaded in green indicate the medication significantly reduces the risk of the specified endpoint vs placebo as part of standard care.

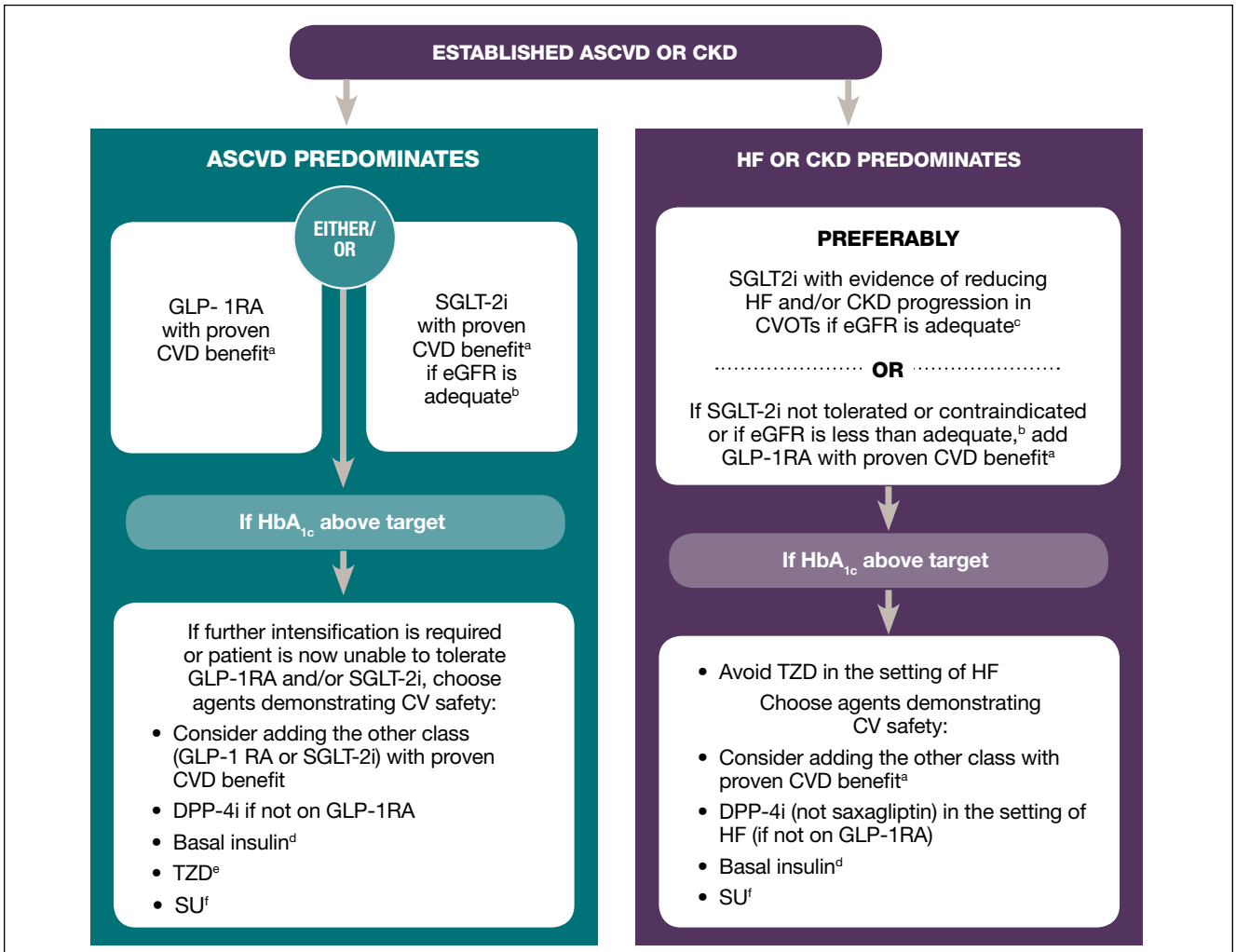
SGLT-2is, as well as amputation (canagliflozin and ertugliflozin), bone fracture (canagliflozin), and bladder cancer (dapagliflozin).

PATIENT SELF-MANAGEMENT

As noted earlier, HF is a largely self-managed disease; thus, it is essential that the patient is willing and able to implement an individualized treatment plan. This requires a collaborative relationship between patient and provider built on effective patient-provider communication and shared decision-making.⁵⁶ A

recent systematic review suggests that utilization of several techniques lead to improved patient-provider communication. These include: (1) asking open-ended questions; (2) utilizing active listening skills; (3) employing motivational interviewing techniques; (4) discussing the most important information first and using the phrase "This is important..." when discussing key points; (5) delivering simple, clear, concrete instructions supported by a written action plan that is appropriate for a patient's culture and health literacy and numeracy; and (6) asking patients to write a list of questions prior to the visit.

FIGURE Recommended therapy for patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease who have inadequate glycemic control with metformin and comprehensive lifestyle management



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; HbA_{1c}, hemoglobin A1c; HF, heart failure; SGLT-2i, sodium glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

^aProven 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.

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

^cEmpagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and reduction in CKD progression in CV outcome trials.

^dDegludec or glargine U-100 have demonstrated CV safety.

^eLow dose may be better tolerated though less well studied for CVD effects.

^fChoose later generation sulfonylurea with lower risk of hypoglycemia.

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A shared decision-making process provides a mechanism to identify patient concerns and develop a treatment plan that addresses those concerns. To accomplish this, the

Agency for Healthcare Utilization and Review has outlined the 5-step SHARE process: (1) seek your patient participation; (2) help your patient explore and compare treatment

options; (3) assess your patient's values and preferences; (4) reach a decision with your patient; and (5) evaluate your patient's decision.³² This approach is applicable to both initiating as well as modifying treatment.

SUMMARY

The rapid evolution in medications available for the treatment of patients with T2DM allows for a more individualized approach to treatment that includes a low incidence of hypoglycemia and weight-neutral or weight-loss effects. Beyond these benefits, evidence now demonstrates that reducing CV events with some GLP-1RAs and SGLT-2is is achievable, thereby enabling greater focus on reducing CV risk as a key treatment objective. For patients with ASCVD alone, a GLP-1RA shown to reduce CV risk is preferred; an SGLT-2i can be considered. For patients with HF or CKD, an SGLT-2i shown to reduce related events is preferred; a GLP-1RA shown to reduce CV risk can be considered. This is a real paradigm shift in our approach to managing patients with T2DM. Finally, the large self-managed nature of HF underscores the importance of individualized treatment through effective communication and the use of shared decision-making. ●

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

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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)

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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.

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 International³⁰ all recommend NSAIDs as first-line treatment for various osteoarthritic conditions. Additionally, guidelines by AAFP³¹ and the American College of Physicians and the American Pain Society³² 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' Association³⁴ 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 al³⁷ 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 treatment⁴⁹ 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 cohort (rate difference, 9.7 deaths/1000 person-years [95%

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). ⁹	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.

^aACR 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.

^bAAFP evidence rating A- Consistent, good-quality patient-oriented evidence

^cAAOS 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.

^dOARSI 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.

^eThe panel strongly recommends that clinicians consider offering the intervention to eligible patients based on benefits clearly outweighing risks.

^fOTA 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.

⁹NATA evidence category A: Recommendation based on consistent and good-quality patient-oriented evidence.

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 Kyeremateng 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 treat-

ment 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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Evolving Issues in Statin Selection

Michael Cobble, MD, FNLA

INTRODUCTION

Statin therapy is the pharmacologic cornerstone for reducing low-density lipoprotein cholesterol (LDL-C) and preventing or slowing progression of atherosclerotic cardiovascular disease (ASCVD).¹ Results from meta-analyses have indicated that statins reduce all-cause and cardiovascular (CV) mortality among patients with risk, including both primary and secondary populations.^{2,3} Statins also have an overall favorable safety profile, although numerous factors can negatively impact statin safety and tolerability.¹

Despite the overall safety and advances in ASCVD prevention with statin therapy, the primary care clinician is faced with optimally managing dyslipidemia among numerous patient populations. This is particularly true in primary prevention patients in which the initiation or intensity of statin therapy is uncertain. Others include those with metabolic syndrome (MetS) or patients on complex medication regimens who are prone to drug-drug interactions and statin-related adverse effects. To aid the clinician, the 2018 American College of Cardiology/American Heart Association Multisociety Guideline on the Management of Blood Cholesterol (2018 ACC/AHA Cholesterol Guideline) provides recommendations on appropriate statin selection and improved patient risk stratification.¹ One such method to better risk stratify patients is the identification of factors that independently increase the risk of ASCVD, so-called risk-enhancing factors. These are supported by epidemiologic data indicating higher overall ASCVD

risk and include common conditions such as chronic kidney disease (CKD), MetS, and chronic inflammatory conditions.¹

2018 ACC/AHA CHOLESTEROL GUIDELINES

Diabetes-specific risk enhancers

Diabetes mellitus has long been established as a major, independent risk factor for ASCVD, although the spectrum of CV risk can vary considerably. Clearly, a young patient newly diagnosed with type 1 diabetes mellitus (T1DM) has less CV risk compared to an older patient with longstanding type 2 DM (T2DM) and additional CV risk factors. A key guideline message specifically notes that among patients 40 to 75 years of age with DM and LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L), a moderate-intensity statin should be initiated without calculating 10-year ASCVD risk. Further, additional risk stratification may be necessary.¹ Notably, the 2018 ACC/AHA Cholesterol Guidelines highlight important DM-specific risk-enhancers that increase ASCVD risk beyond DM and are independent of traditional CV risk factors.¹ These are: (1) disease duration ≥ 20 years for T1DM and ≥ 10 years for T2DM; (2) albumin to creatinine ratio ≥ 30 mcg/mg; (3) estimated glomerular filtration rate < 60 mL/min/1.73 m²; (4) retinopathy; (5) neuropathy; and (6) ankle-brachial index < 0.9 . Evaluating the patient for duration of DM and the presence of common long-term complications associated with DM will provide further risk stratification and help determine intensity of treatment.

Metabolic syndrome—impact on individualizing therapy

MetS is a clustering of conditions that markedly increases the risk of ASCVD, DM, and all-cause mortality (TABLE 1).¹ Thereby, MetS is a risk-enhancing factor for ASCVD. Insulin resistance is considered an underlying cause of MetS and is strongly associated with prediabetes, DM, obesity, visceral adiposity, nonalcoholic steatohepatitis, and systemic inflammation.^{4,5} Rates of MetS closely parallel those of obesity in the United States, having increased dramatically in the past few decades. Currently, the prevalence of MetS is approximately one-third of US adults, although this may be an underestimation given insufficient screening rates.¹

MetS is also closely linked with other conditions including autoimmune diseases (eg, systemic lupus erythematosus, rheumatoid arthritis), CKD, and human immunodeficiency

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TABLE 1 General risk-enhancing factors for additional risk stratification¹

- **Family history of premature ASCVD** (males, age <55 years; females, age <65 years)
- **Primary hypercholesterolemia** (LDL-C 160-189 mg/dL; non-HDL 190-219 mg/dL)*
 - **Metabolic syndrome** (increased waist circumference, elevated triglycerides [≥ 150 mg/dL], elevated blood pressure, elevated fasting blood glucose, and low HDL-C [< 40 mg/dL in men; < 50 mg/dL in women] are factors; tally of 3 makes the diagnosis)
- **Chronic kidney disease** (eGFR 15-59 mL/min/1.73 m², with or without albuminuria; not treated with dialysis or kidney transplant)
- **Chronic inflammatory conditions** such as psoriasis, RA, HIV/AIDS
- **History of premature menopause (before age 40 years) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia**
- **High-risk race/ethnicities** (eg, South Asian ancestry)
- **Lipid/biomarkers:** associated with increased ASCVD risk
 - **Persistently* elevated, primary hypertriglyceridemia** (≥ 175 mg/dL)
 - **If measured:**
 - **Elevated high-sensitivity C-reactive protein** (≥ 2.0 mg/L)
 - **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥ 50 mg/dL constitutes a risk-enhancing factor especially at higher levels of Lp(a)
 - **Elevated apolipoprotein B** ≥ 130 mg/dL: A relative indication for its measurement would be triglyceride ≥ 200 mg/dL. A level ≥ 130 mg/dL corresponds to an LDL-C > 160 mg/dL and constitutes a risk-enhancing factor
 - **Ankle-brachial index** < 0.9

Abbreviations: AIDS, acquired immunodeficiency syndrome; ASCVD, atherosclerotic cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; RA, rheumatoid arthritis.

*Optimally, 3 determinations.

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virus (HIV).⁶⁻⁸ For autoimmune diseases, the link may be the result of shared inflammatory mediators.⁸ The etiology for CKD is less clear, but renal injury may be secondary to insulin resistance, oxidative stress, and the proinflammatory state characteristic of MetS.⁶ The chronic inflammatory burden and insulin resistance inherent with HIV likely explain the association.⁷ The multiple metabolic abnormalities and the chronic inflammatory state observed with MetS predispose patients to atherothrombotic events. Such individuals, especially those that are older, commonly have an ASCVD risk score between 7.5% and 20% (intermediate risk), with the likelihood of additional risk-enhancing factors (eg, elevated high-sensitivity C-reactive protein) in addition to MetS. The initiation of moderate-intensity statin therapy, along with lifestyle changes, is reasonably justified in this patient type.¹

Risk-enhancing factors for clinician-patient risk discussion

Risk-enhancing factors can aid in risk stratification and should trigger discussion with the patient (TABLE 1).¹ A common scenario involves evaluating a complex patient who has not had a CV event, but who has risk-enhancing factors. While the ASCVD risk score indicates the patient is at intermediate

risk of an ASCVD event, the presence of risk-enhancing factors indicates greater risk. In this scenario, it is recommended to acknowledge the risk-enhancing factors and engage in a clinician-patient discussion to reduce CV risk through lifestyle management and possible initiation or intensification of statin therapy.¹

Risk-enhancing factors that have been identified primarily from epidemiologic data elevate ASCVD risk by varying levels. The degree of lifetime risk is typically proportional to the magnitude of the risk-enhancing factor. For example, patients with vs without MetS have a relative risk (RR) for CV events of 1.78, while patients with both MetS and DM have a RR of 2.35.^{9,10} Similar data reported with chronic inflammatory conditions show the RR for major cardiometabolic diseases is 1.25 for psoriasis, 1.7 for rheumatoid arthritis and 6.4 for systemic lupus erythematosus.¹¹ Finally, CV mortality follows the progression of CKD. The RR for CV events is 1.38 in patients with an estimated glomerular filtration rate (eGFR) of 45-59 mL/min/1.73 m² compared to 3.29 for an eGFR of 15-29 mL/min/1.73 m².¹² Other notable conditions and RR for CV events include early menopause (1.32),¹³ a history of preeclampsia/eclampsia (2.28),¹⁴ and a family history of premature ASCVD (~2-fold),¹⁵ while the presence of HIV is associated with a nearly 3-fold increase in coronary heart

TABLE 2 Key take-home messages to reduce ASCVD through cholesterol management¹

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.
2. In patients with clinical ASCVD, reduce LDL-C with high-intensity statin therapy or maximally tolerated statin therapy.
3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL to consider addition of nonstatins to statin therapy.
4. In patients with severe primary hypercholesterolemia (LDL-C \geq 190 mg/dL), without calculating 10-year ASCVD risk, begin high-intensity statin therapy.
5. In patients 40 to 75 years of age with DM and LDL-C \geq 70 mg/dL, start moderate-intensity statin therapy without calculating 10-year ASCVD risk.
6. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician-patient risk discussion before starting statin therapy.
7. In adults 40 to 75 years of age without DM and with LDL-C levels \geq 70 mg/dL, at a 10-year ASCVD risk of \geq 7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.
8. In adults 40 to 75 years of age without DM and 10-year risk of 7.5% to 19.9%, risk-enhancing factors favor initiation of statin therapy.
9. In adults 40 to 75 years of age without DM and with LDL-C \geq 70 mg/dL to 189 mg/dL, at a 10-year ASCVD risk of \geq 7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.
10. Assess adherence and percentage response to LDL-C-lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol.

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disease.¹⁶ These findings stress the importance of a comprehensive patient evaluation and incorporating risk-enhancing factors into clinical practice.

Top 10 take-home messages

An important section of the 2018 ACC/AHA Cholesterol Guidelines is a summary of 10 major take-home messages to reduce the risk of ASCVD through cholesterol management (**TABLE 2**).¹ The first message emphasizes a heart healthy lifestyle across the life course. The next 3 messages focus on those with ASCVD or severe hypercholesterolemia and the importance of a high-intensity or maximally tolerated statin to lower LDL-C by \geq 50%. The addition of non-statin therapies (eg, ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors) may be considered when LDL-C is \geq 70 mg/dL in very high-risk patients or those with high baseline LDL-C. Another major point is that for most patients with DM, a moderate-intensity statin is appropriate unless multiple risk factors are present, in which case a high-intensity statin can be implemented to reduce LDL-C by \geq 50%.

The remaining take-home messages involve patients for primary prevention and illustrate populations where clinicians often struggle to accurately identify ASCVD risk and the appropriate therapy. Tools such as the ACC/AHA ASCVD risk estimator can identify 10-year risk (<http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/>). However, further risk stratification is often necessary to enhance ASCVD risk estimates and guide therapy. The ASCVD risk estimator is a robust tool that predicts

population risk, but is limited when estimating individual risk.¹ Conversely, identifying risk-enhancing factors (**TABLE 1**) can influence individual risk, and confirms a higher risk state. The final take home message is to assess adherence to lifestyle/medications and optimal percentage response for LDL-C goal achievements in 4 to 12 weeks, then every 3 to 12 months as needed.

CONTRIBUTION OF STATIN THERAPY TO DIABETES MELLITUS

New-onset vs newly diagnosed

In 2012, the US Food and Drug Administration (FDA) released a statement indicating an association with statin therapy and reports of increased glycosylated hemoglobin (A1c) and fasting serum glucose.¹⁷ That same year, the European Medicines Agency (EMA) reported an increased risk of new onset diabetes (NOD) in patients already at risk for DM and receiving statin therapy.¹⁸ Multiple studies have since confirmed this relationship and provided additional data to guide practice.

Screening patients to determine baseline glycemic values is recommended prior to initiating a statin.¹⁹ This is particularly important among patients at risk for DM, such as those with MetS since, if baseline values are not established and glucose elevations are observed poststatin initiation, the patient and practitioner may inherently assume the impaired values are statin-related. Screening is further supported by population data, as approximately 25% of US adults with T2DM and 90% of those with prediabetes are not aware of their glucose impairment.^{20,21}

Statin-associated diabetes mellitus via unclear mechanism(s)

A host of mechanisms have been proposed to explain the association between statin therapy and NOD. Those discussed most commonly include decreased glucose transporter 4 (GLUT 4) expression, diminished levels of coenzyme Q10 (CoQ10), blocking calcium channels in pancreatic β cells, altering adiponectin concentrations, and single nucleotide polymorphisms (SNPs) resulting in inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR).²²⁻²⁴ Statin therapy can impact these processes, which prevent cellular glucose uptake (CoQ10 and GLUT 4), limit insulin secretion (blocking calcium channel), and mitigate insulin sensitivity by reducing adiponectin levels.²²⁻²⁴ Genetic analyses have also demonstrated certain HMGCR SNPs are associated with glucose impairment.²³ Overall, the mechanism(s) responsible for the dysglycemic effects of statins are likely multifactorial, and vary among individual statins.

Modest increase in risk and populations more likely affected

The overall increase in NOD with statin therapy is generally considered to be modest, but data are mixed. Numerous studies have also been performed identifying the associated risk factors. Individuals with multiple features of MetS may be more prone to developing NOD with statin use.¹⁹ Other potential risk factors include female gender, older adults (~65-75 years), Asian ethnicity, extended duration of statin use, and those with a family history of DM.²²

In 2010, a meta-analysis was performed of 13 major randomized controlled trials (RCTs) comparing statin or placebo and incident DM.²⁵ Overall, a 9% increased risk for incident DM was noted with statin therapy. This study, and other similar analyses, concluded that statin therapy is associated with a small but significant risk of NOD.¹⁹ Conversely, a 2015 meta-analysis of observational studies demonstrated a stronger association of statin therapy with NOD (RR, 1.44; 95% confidence interval [CI], 1.31-1.58) than that observed from RCT data.²⁶ The authors of the meta-analysis emphasized rigorous monitoring for NOD with those prescribed statins, especially among patients with risk factors for DM. Limitations of the meta-analysis based on RCTs include a short follow-up period, underpowered sample size, and lack of prespecified diagnostic criteria for DM.

Differences among individual statins

Statin-associated NOD is considered a class effect by the FDA.¹⁷ Most data indicate that statin dose and potency play a role with NOD, whereas other data indicate certain agents may be less diabetogenic and demonstrate no dose depen-

dency.^{22,27} One analysis noted an increased risk of NOD with rosuvastatin (hazard ratio [HR]=1.41; 95% CI, 1.31-1.52), atorvastatin (HR=1.23; 95% CI, 1.19-1.27), and simvastatin (HR=1.15; 95% CI, 1.05-1.25), but only minimal association with fluvastatin (HR=1.04; 95% CI, 0.91-1.18).²⁸ Similarly, another meta-analysis noted the following odd ratios of statin associated NOD: rosuvastatin: (1.17; 95% CI, 1.02-1.35), simvastatin (1.13; 95% CI, 0.99-1.29), atorvastatin (1.13; 95% CI, 0.94-1.34), pravastatin (1.04; 95% CI, 0.93-1.16), lovastatin (0.98; 95% CI, 0.69-1.38), and pitavastatin (0.74; 95% CI, 0.31-1.77), with atorvastatin 80 mg having the highest associated risk (1.34; 95% CI, 1.14-1.57).²⁹ Another study analyzed rates of NOD among Asian patients with a recent acute myocardial infarction and no DM at baseline, who were subsequently prescribed moderate-intensity statin therapy.³⁰ After a follow up period of up to 3 years, significantly more patients receiving rosuvastatin (10.4%) and atorvastatin (8.4%) had experienced NOD compared to pitavastatin (3%). Finally, the efficacy and safety of pravastatin and pitavastatin were compared in a RCT involving subjects with HIV.³¹ These specific agents were evaluated due to the challenge of treating dyslipidemia in the HIV population because of drug interactions. Neither pravastatin or pitavastatin are dependent upon the cytochrome P450 system for primary metabolism. The trial demonstrated that both treatments had neutral effects on glycemic indices in a population that is at greater risk for glycemic abnormalities and NOD.

Although data are accumulating regarding the association of statins with NOD, findings remain inconclusive. Nonetheless, statements from the FDA and EMA both indicate the risk-benefit ratio highly favors the utilization of statin therapy in at-risk patients.^{17,18} Further, the National Lipid Association recommends no changes to clinical practice, except to monitor glycemic indices before and after statin initiation.¹⁹ Finally, the Diabetes Prevention Program demonstrated the importance of modest weight loss and physical activity on glucose metabolism, as those with prediabetes were nearly 60% less likely to develop T2DM with a structured lifestyle program.³² These findings further support the importance of diet and exercise as the foundation for ASCVD risk reduction and the likelihood of limiting NOD when utilizing statin therapy.¹

EFFECT OF STATIN THERAPY ON BODY WEIGHT

Genetic variants in population studies have suggested that certain HMGCR SNPs are associated with an increase in body weight and risk of T2DM. Since statins pharmacologically inhibit HMGCR, they, too, may have similar metabolic effects. Swerdlow et al investigated this relationship both from observational data (genetic analysis) and among statin users from RCTs.²³ The investigators found that the HMGCR

SNPs and statin treatment were each associated with higher body weight and risk of T2DM. A second study utilized a different approach and evaluated the impact of atorvastatin and pitavastatin on non-HDL-C and the influence of body size.³³ Similar reductions ($P=.456$) in non-HDL-C were noted for atorvastatin (40.3%) and pitavastatin (39%), but atorvastatin was most efficient among those with lower weight (correlation coefficient [r]=0.32, $P=.006$), body mass index ($r=0.279$, $P=.022$), and waist circumference ($r=0.33$, $P=.034$), whereas pitavastatin demonstrated a consistent reduction in non-HDL-C regardless of weight ($r=0.04$, $P=.762$), waist circumference ($r=0.04$, $P=.822$), and body mass index ($r=0.05$, $P=.736$). Collectively, these data suggest further analyses are needed to better elucidate the relationship between individual statins and body weight, and response to therapy.

STATIN-ASSOCIATED MUSCLE SYMPTOMS

Patient-reported musculoskeletal complaints are the major barrier to maintaining statin therapy.³⁴ Approximately 10% of those prescribed statins in the United States stop therapy because of such complaints.³⁵ The incidence of muscle symptoms without elevated creatine kinase in major RCTs is nearly identical between subjects receiving a statin and placebo.³⁵ This strongly suggests that reported muscle symptoms are typically not statin-related. Although challenging, the AHA stresses the importance of restarting statin therapy, especially in those at high risk for ASCVD.

A thorough patient evaluation is essential to identify true intolerance prior to reinitiating a statin. Unexplained muscle symptoms with symmetric distribution occurring shortly after initiation are more likely statin-related.³⁴ In such cases, several approaches can be implemented, including utilization of a different statin and alternative dosing strategies using a statin with a long elimination half-life (ie, atorvastatin, rosuvastatin, pitavastatin), with gradual titration from once weekly to every other day dosing.³⁶ Other strategies include serum vitamin D repletion and CoQ10 supplementation. Although support for each is limited, anecdotal reports indicate a possible role in practice.³⁶ Supplementation with CoQ10 may possibly reverse or prevent statin-associated muscle symptoms since statins reduce plasma levels of CoQ10,³⁷ with deficiencies of CoQ10 resulting in myalgia.³⁸ The choice of statin may matter since individual statins appear to have different effects on plasma CoQ10 levels. Although not designed to evaluate muscle symptoms, a 12-week RCT demonstrated that, despite comparable LDL-C reductions, pitavastatin lowered CoQ10 plasma levels significantly less than atorvastatin and rosuvastatin.³⁹ These data are consistent with an earlier study, noting significant reductions in CoQ10 plasma levels with atorvastatin, but not pitavastatin, even though

LDL-C reductions were similar.⁴⁰ Finally, regardless of the approach or statin utilized, direct conversations and incorporating shared decision-making when rechallenging patients are essential.

SUMMARY

Statin therapy continues to be the pharmacologic foundation for LDL-C reduction and ASCVD prevention. However, challenges remain with accurately identifying and stratifying ASCVD risk, especially in primary prevention populations. Clinicians must be aware of and incorporate risk-enhancing factors into practice for each individual patient to further guide treatment. Statin selection is also critical. For most patients, moderate- to high-intensity statin therapy is recommended. Further, understanding differences among individual statins is essential for proper selection. Utilizing a statin with minimal drug interactions and properties that do not aggravate risk-enhancing factors, or more importantly, effectively addressing such factors on an individual patient basis, will likely result in improved safety and patient tolerability. Monitoring adherence to lifestyle and medication use as well as LDL-C response is crucial. Most importantly, clinicians must engage the patient when discussing these factors to appropriately risk stratify and individualize statin therapy for optimal therapeutic responses. ●

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Identification and Management of Insomnia in Alzheimer's Disease

Thomas Roth, PhD; Stephen Brunton, MD, FAAFP

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading the review article on insomnia in patients with Alzheimer's disease (AD), participants should be able to:

- Describe the association of insomnia with AD.
- Characterize the burden of insomnia in AD on patients and their family/caregivers.
- Prescribe medication for insomnia in patients with AD based on existing evidence and current recommendations.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of insomnia in patients with AD.

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THE BURDEN OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common cause of dementia, affecting an estimated 5.7 million Americans; nearly two-thirds are women.¹ The vast majority of people

with AD are aged ≥ 65 years.¹ After age 85 years, 34% of people have AD or related dementia.² Most people with AD survive an average of 4 to 8 years following diagnosis, although some live as long as 20 years. AD is the only top 10 cause of death

that cannot be prevented or cured.¹ In 2017, AD was the 15th leading cause of disability-adjusted life years worldwide.³

Beyond progressive cognitive impairment, people with AD are at increased risk of neuropsychiatric symptoms such as delusions and hallucinations, depressive symptoms, wandering, anxiety, disturbances in diurnal rhythm, and agitation with or without aggression.^{4,5} Apathy is more common in those with AD onset before age 65 years.⁴ Neuropsychiatric symptoms, particularly delusions, may be associated with a more severe course of AD.⁶

Bodily injury, particularly related to falls, is common in people with AD, often resulting in fractures.^{7,8} Falls are often observed during the nighttime hours, in part because individuals with AD commonly suffer from insomnia, sometimes resulting in reversal of their sleep-wake periods.^{9,10} Insomnia has been shown to contribute to cognitive decline, as well as early nursing home placement.¹

The chronic nature of the illness contributes significantly to the public health impact of AD because much of that time is spent in a state of disability and dependence. Thus, the burden is not only the patient's, but is shared with society in general and the family and caregivers in particular. AD rose from the 12th most burdensome disease or injury in 1990 to the 6th in 2016, in part due to its rising mortality rate.¹¹ In terms of years lived with disability, AD rose from the 23rd to the 19th during the same period. In 2017, caregivers provided an estimated 18.4 billion hours of unpaid care, valued at \$232 billion.¹² The total lifetime cost of care for a person with dementia was estimated at \$341,840 in 2017, 70% of which is borne by the family, largely through providing unpaid care.¹³ Families and caregivers also experience emotional stress and depression, new or exacerbated health problems, including physical difficulties and financial challenges.¹⁴⁻¹⁹ Insomnia often emerges among caregivers when the need to provide nighttime care becomes frequent.^{20,21} One-third of family caregivers report that their own health deteriorated since becoming a caregiver.¹

CASE SCENARIO #1

A 63-year-old woman was seen by her primary care provider for a 1 month follow up visit for her mild obstructive sleep apnea (OSA). While she reports overall better sleep using her continuous positive airway pressure (CPAP) machine, she experiences disrupted sleep and daytime fatigue; she also reports feeling less motivated with her daily routine. Her history reveals frequent difficulty falling asleep as well as falling back to sleep. Her daughter has accompanied her and reports that her mother has increasing difficulty 'finding her words'.

ASSOCIATION OF INSOMNIA WITH ALZHEIMER'S DISEASE

While a person is awake, extracellular levels of metabolites produced by neuronal activity, such as amyloid- β and tau proteins, increase in the brain. During restorative sleep, these metabolites are cleared from the brain through the glymphatic system.²² When the sleep-wake cycle is disrupted, clearance of these metabolites is diminished.^{23,24} Accumulation of amyloid- β and tau proteins hastens the formation of the characteristic amyloid plaques and neurofibrillary tangles observed in people with AD.

Accumulating evidence supports the view that a bidirectional association exists between sleep disorders (eg, insomnia) and AD, beginning before the clinical onset of AD.²⁴⁻²⁶ Increased deposition of amyloid- β causes disruption of the sleep-wake cycle,²⁵ including poorer sleep quality and shorter sleep duration.²⁷

Poor sleep quality, as evidenced by decreased non-rapid eye movement (non-REM) sleep slow wave activity, is associated with amyloid- β deposition, as well as intracellular aggregation of tau in the neocortex.²⁸ Sleep deprivation and sleep fragmentation also increase the accumulation of amyloid- β and tau proteins in the brain.²⁹ In fact, a positive association between levels of sleep fragmentation at baseline and rate of cognitive decline has been demonstrated (hazard ratio 1.22; 95% confidence interval [CI], 1.03-1.44; $P=.02$ per 1 standard deviation increase in sleep fragmentation).³⁰

Disruptions in the circadian system appear to interact with sleep disruption, possibly via orexin and melatonin, to increase progression of AD.²⁹ Disruption of the sleep-wake cycle is characterized by increased levels of orexin, a wake-promoting neuropeptide. Animal studies in which the orexin gene is knocked out show marked decrease in amyloid- β deposition in the brain and an increase in sleep time.^{31,32}

Other factors thought to serve as mediators between sleep deprivation and AD include reactive oxygen species and glymphatic system dysfunction, among others.²⁵

Further evidence supporting an association between insomnia and dementia is provided by a meta-analysis of 5 community-based prospective cohort studies. The analysis showed an increased risk (relative risk 1.53; 95% CI, 1.07-2.18) of developing dementia in people with a preexisting diagnosis of insomnia.³³ More recently, a case-control study of 51,734 individuals diagnosed with primary insomnia without a dementia diagnosis at baseline showed a 2.14-fold (95% CI, 2.01-2.29) increase in dementia risk.³⁴

THE BURDEN OF INSOMNIA IN ALZHEIMER'S DISEASE

CASE SCENARIO #2

A 71-year-old man is seen for his annual physical. Although he reports that he feels fine and his health has not changed over the past year, his wife reports that 'he doesn't seem like his old self'. He does admit to waking up at night several nights per week, but attributes this to a need to urinate. He further reports difficulty falling back to sleep after these events.

Sleep changes are more common in later stages of AD, although they are observed in early stages.³⁵ People with AD often experience a shift in their sleep-wake cycle, experiencing insomnia during the night, ie, waking up more often and staying awake longer, while napping during the daytime. In the late stages of AD, people spend about 40% of their time in bed at night awake and a significant part of their day napping. In extreme cases, people may have a complete reversal of the usual daytime wakefulness-nighttime sleep pattern. Restlessness or agitation is common, particularly in late afternoon or early evening, called sundowning. Those who cannot sleep at night may wander, be unable to lie still, or yell or call out. Falling during the night is common and contributes to an increased risk for bodily injury, particularly fractures. The health consequences of insomnia to the person with AD—and the caregiver's inability to provide the needed care—can contribute to early nursing home placement.³⁶

Overall, family caregivers generally experience a significant physical and psychological burden, as well as a financial burden.¹ In addition to negatively impacting the family caregiver's sleep,^{20,21} the stress of providing dementia care increases the caregiver's susceptibility to disease and health complications.¹⁷ According to the Alzheimer's Association, 74% of caregivers of people with AD or other dementia reported that they were "somewhat concerned" or "very concerned" about their own health.¹ Nearly half of dementia caregivers are in a high-burden situation, which is less than cancer caregivers. However, where cancer caregivers often provide care for short periods of time, dementia caregivers tend to provide care for a long period of time.³⁷

ASSESSING COMORBIDITIES IN PEOPLE WITH ALZHEIMER'S DISEASE

The high prevalence and consequences of insomnia in people with AD necessitate a thorough medical examination, including sleep history. It is suggested to include the caregiver or family member so that an accurate history can

be obtained. Questions should be asked to identify sleep patterns such as:

- When do you go to sleep?
- When do you arise?
- How many times a night do you awaken?
- When you awaken, how long does it take you to fall asleep?
- What percent of the time you spend in bed intending to sleep do you actually sleep?

In addition, questions should be asked about conditions that may make sleep problems worse, such as:

- Do you snore?
- Has anyone observed that you have episodes where you stop breathing?
- Do you feel a need to move your legs when at rest?
- Do you move around in bed a lot?
- Are you depressed?

Obstructive sleep apnea (OSA) occurs in half of patients with AD, with the OSA severity associated with dementia severity.³⁸⁻⁴⁰ Restless leg syndrome is thought to occur in about 5% of patients with AD⁴¹ and can have a profound impact on sleep. Depression occurs in up to 40% of people with AD, particularly in the early to middle stages of the disease.¹

Treatment of other conditions that affect sleep should be optimized, including chronic obstructive pulmonary disease, allergies, a pain disorder, and anxiety, as this may reduce the symptoms of insomnia, thereby lessening the disease burden for both patient and caregiver.

TREATMENT OF INSOMNIA

Given the absence of effective disease-modifying treatment options for AD and the long duration of symptoms and disability, safety for the patient, as well as the caregivers, is a consideration for overall patient management. This particularly relates to the management of other conditions, eg, insomnia, so as to avoid the use of medications that might result in complications, such as falls or further cognitive impairment.

As a first step, conditions that may contribute to insomnia should be identified and appropriate action taken.⁴² Eating or drinking, particularly alcohol, several hours before sleep should be avoided. A daily schedule with similar daily wake and sleep times and quiet time should be established. Light exposure in the pre-sleep period and during the night needs to be avoided. In contrast, morning sunlight exposure and exercise are important. Bright light therapy is thought to be helpful, but benefits may be affected by treatment

intensity and duration, as well as time of year.⁴³ Poor sleep habits, such as irregular sleep hours, should be corrected.³⁵ If possible, medications should be avoided that might impair sleep, eg, alpha-blockers, beta-blockers, corticosteroids, serotonin selective reuptake inhibitors, and angiotensin converting enzyme inhibitors. Diseases that contribute to insomnia should be treated initially with nonpharmacologic options, if possible. For example, acute or subacute low back pain should be managed initially with superficial heat, massage, acupuncture, or spinal manipulation.⁴⁴

When these initial strategies are ineffective in improving sleep, further intervention may be warranted. In patients without AD, cognitive behavioral therapy (CBT) is recommended as the first-line approach for insomnia due to its effectiveness and safety.⁴² The major interventions in terms of mediating efficacy, ie, decreasing wake time in bed, are sleep restriction therapy (limiting time in bed) and stimulus control (getting out of bed when not sleeping). Both of these may increase sleepiness while awake, which can further exacerbate compromised alertness in patients with AD. Moreover, stimulus control, getting out of bed repeatedly in patients with AD, may increase the risk of falls. Therefore, while CBT is generally an effective treatment for insomnia, its efficacy and safety in people with AD has not been established and should, therefore, be used with caution in this population.

Pharmacotherapy

When CBT does not achieve its goals, short-term pharmacotherapy should be considered to reestablish a regular sleep pattern. However, there is little evidence from clinical trials to guide the selection of pharmacotherapy for insomnia in people with AD.⁴² A 2016 Cochrane Review found only 6 randomized clinical trials that had the primary aim of improving sleep in people with dementia who had insomnia.⁴⁵ The reviewers found no evidence to support the use of melatonin ≤ 10 mg/day or ramelteon 8 mg/day in insomnia associated with AD, with some evidence to support the use of trazodone 50 mg/day. There were no reports of serious adverse effects with melatonin, ramelteon, or trazodone in the trials analyzed. As noted by the reviewers, uncertainty remains about the balance of benefits and risks associated with benzodiazepine and most "non-benzodiazepine" hypnotics such as eszopiclone, zaleplon, and zolpidem, which are commonly used for insomnia in people with dementia, including AD.

In 2012, the American Geriatrics Society sought to provide guidance regarding the use of medications in older adults.⁴⁶ To do this, a systematic review of clinical trials, observational studies, and systematic reviews and meta-analyses involving adults aged ≥ 65 years was conducted. The

guidance, called the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, was updated in 2015⁴⁷ and again in 2019.⁴⁸ According to the 2019 Beers Criteria, several of the medication classes commonly used to treat insomnia should be avoided in older adults, many because of their anticholinergic properties and/or prolonged sedation. These include first-generation antihistamines, some antidepressants, barbiturates, benzodiazepines, and other benzodiazepine receptor agonists (**TABLE**).⁴⁸

According to the Beers Criteria, these same classes of medications (except barbiturates) should be avoided in older adults with dementia or cognitive impairment. First-generation antihistamines (including those found in OTC sleep aids) and many antidepressants should be avoided due to their anticholinergic and central nervous system effects. Benzodiazepines are to be avoided because they cause dizziness and prolonged sedation. Moreover, their use in people with AD is associated with an increased risk of falling, resulting in fractures.⁴⁹⁻⁵¹ There is a black box warning for benzodiazepines regarding the risk of profound sedation, respiratory depression, coma, and death with concomitant opioid therapy. Antipsychotics are associated with greater risk of stroke and mortality in older people with dementia.⁴⁸ One case series of 6790 people with at least one prescription for an antipsychotic and a stroke found that the rate ratio for stroke was 3.5 for those with dementia and 1.41 for those without dementia.⁵² There is a black box warning of increased mortality in elderly patients with dementia-related psychosis treated with antipsychotics. The benzodiazepine receptor agonists eszopiclone, zaleplon, and zolpidem also should be avoided due to adverse events similar to classical benzodiazepines; in addition, they provide minimal improvement in sleep latency and duration in the AD population.⁴⁸

Not included in the Beers list of medications to avoid in older adults, including those with dementia or cognitive impairment, are doxepin ≤ 6 mg/day, the melatonin receptor agonist ramelteon, and the orexin receptor antagonist suvorexant. According to the Beers Criteria, the safety profile of doxepin ≤ 6 mg/day is comparable to placebo.

Ramelteon has not been prospectively investigated for the treatment of insomnia in patients with AD, but there are 5 case reports in this setting. Each showed improvement in behavioral and psychological symptoms, primarily delirium, with ramelteon 8 mg once daily at bedtime in patients with AD and disrupted sleep-wake cycle.⁵³⁻⁵⁵ Ramelteon is not recommended in people with severe sleep apnea since it has not been studied in this population.⁵⁶

Suvorexant is the first medication to be systematically investigated in a phase 3 randomized, double blind clinical trial for the treatment of insomnia in people with mild-

TABLE Potentially inappropriate medications that are often used for insomnia in older adults⁴⁸

Class/medications	Explanation
Antihistamines, first-generation Brompheniramine Diphenhydramine (oral) Carbinoxamine Doxylamine Chlorpheniramine Hydroxyzine Clemastine Meclizine Cyproheptadine Promethazine Dexbrompheniramine Pyrilamine Dexchlorpheniramine Triprolidine Dimenhydrinate	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity. [Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate.]
Antidepressants Amitriptyline Imipramine Amoxapine Nortriptyline Clomipramine Paroxetine Desipramine Protriptyline Doxepin >6 mg/d Trimipramine	Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≤ 6 mg/day) comparable with that of placebo.
Antipsychotics, first- and second-generation	Increased risk of cerebrovascular accident (stroke) and greater rate of cognitive decline and mortality in people with dementia. Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others.
Barbiturates Amobarbital Pentobarbital Butabarbital Phenobarbital Butalbital Secobarbital Mephobarbital	High rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages.
Benzodiazepines, short- and intermediate-acting Alprazolam Oxazepam Estazolam Temazepam Lorazepam Triazolam	Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents; in general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults.
Benzodiazepines, long-acting Chlordiazepoxide Flurazepam Clonazepam Quazepam Clorazepate Diazepam	May be appropriate for seizure disorders, rapid eye movement sleep behavior disorder, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, and perioperative anesthesia.
Non-benzodiazepine, benzodiazepine receptor agonists Eszopiclone Zaleplon Zolpidem	Have adverse events similar to benzodiazepines in older adults (eg, delirium, falls, fractures); increased emergency room visits/hospitalizations; motor vehicle crashes; minimal improvement in sleep latency and duration.

Source: Fick DM, Semla TP, Steinman M, et al. American Geriatrics Society 2019 Updated AGS Beers Criteria[®] for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2019;67(4):674-694; John Wiley & Sons Inc. © 2019 The American Geriatrics Society.

to-moderate AD (N=284).⁵⁷ Following screening and run-in periods, patients were randomized to suvorexant 10 mg or placebo daily for 4 weeks. Suvorexant could be increased to

20 mg daily based on clinical response. From a mean baseline of 278 minutes and 274 minutes, mean total sleep time increased 73.4 minutes and 45.2 minutes in patients treated

with suvorexant and placebo, respectively ($P < .005$). The mean wake after persistent sleep onset time decreased 41.8 minutes with suvorexant and 32.5 minutes with placebo ($P = .01$). An adverse event was experienced by 22.5% of patients treated with suvorexant and 16.1% of patients treated with placebo. One patient in each group discontinued treatment due to an adverse event. Mild-to-moderate somnolence was the most common adverse event and was observed in 4.2% and 1.4% of suvorexant and placebo patients, respectively. Other adverse events included headache (3.5% vs 4.2%), dry mouth (2.1% vs 0.7%), and falls (2.1% vs 0%). Prior to initiating suvorexant, the effect on respiratory function should be considered in those with compromised respiratory function.⁵⁸

SUMMARY

Alzheimer's disease is an increasingly common, highly burdensome, and ultimately fatal disease. In addition to neuropsychiatric disorders, disruption of the sleep-wake cycle is common in people with AD, and may be caused by as well as contribute to AD itself. Assessing for the presence and consequences of insomnia and other sleep-related disorders is important. Little investigation in clinical trials has been undertaken to evaluate the safety and efficacy of medications for insomnia in people with AD, although the results of a trial of suvorexant in this setting have recently been reported at a national meeting but not yet published. The Beers Criteria for Potentially Inappropriate Medication Use in Older Adults recommends that many classes of medications used to treat insomnia not be used in older adults with dementia or cognitive impairment. These are first-generation antihistamines (including OTC sleep aids), some antidepressants, benzodiazepines, and "non-benzodiazepines." ●

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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-

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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

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

- | |
|---|
| <p>A. At least five attacks fulfilling criteria B-D</p> <p>B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)¹</p> <p>C. Either or both of the following:</p> <ol style="list-style-type: none"> 1. at least one of the following symptoms or signs, ipsilateral to the headache: <ol style="list-style-type: none"> 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 <p>D. Occurring with a frequency between one every other day and eight per day²</p> <p>E. Not better accounted for by another ICHD-3 diagnosis.</p> |
|---|

[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.]

¹During 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.

²During 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	 <p>Unilateral around the eye, above the eye, or near the temple</p>
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 dur-

ing 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/AHSPfilesIssue4.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-cephalgias/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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Patient-Centric Care of Diarrhea-Predominant Irritable Bowel Syndrome

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading the review article on diarrhea-predominant irritable bowel syndrome (IBS-D), participants should be able to:

- Describe the evidence indicating that irritable bowel syndrome (IBS) is both a brain-gut and a gut-brain disorder
- Describe the role of the Rome IV criteria, colonoscopy, and other tests used to diagnose IBS
- Implement strategies to facilitate provider understanding of patient concerns and disease burden
- Individualize treatment for IBS-D based on current evidence-based guidelines to address patient concerns and improve quality of life

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of irritable bowel syndrome – diarrhea predominant.

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SUPPORTER

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“With IBS-D, there’s always that sense of dread. I know it’s going to happen again, but I don’t really know when or where it’s going to happen again. When it does, I could end up in the bathroom for a good long while doubled over in agony. And after a flare, I suffer from extreme lethargy. It leaves my body so drained that I literally can’t do any-

thing. If I’m at work, I have to go home. If I’m at home, I go straight to bed.”

JO C.
IBS-D SUFFERER

PATIENT BURDEN RELATED TO IBS

The quote from Jo, a patient with irritable bowel syndrome (IBS) and diarrhea symptoms, nicely illustrates the often-overlooked fact that health-related quality of life is

diminished in patients with IBS. Patients with diarrhea-predominant irritable bowel syndrome (IBS-D) have significantly lower self-esteem compared to both healthy controls¹ and patients with constipation-predominant IBS (IBS-C).² Although surprising to many health care providers, patients with IBS-C, IBS-D, or IBS-mixed (IBS-M) report significantly greater symptom severity than patients with inflammatory bowel disease.³ A survey involving 1102 people with IBS-D showed that one-third experience mild symptoms, 50% moderate symptoms, and 13% severe symptoms.⁴ Approximately one-quarter experience daily or near daily symptoms, while more than one-quarter report their symptoms as very or extremely bothersome.

For patients with IBS-D, symptoms that most affect quality of life are urgency (64%), gas (41%), bloating (39%), fatigue (33%), gastroesophageal reflux disease (14%), and nausea (10%).⁵ In contrast, patients with IBS-C report the most bothersome symptoms are abdominal pain/bloating (32%), sensation of incomplete evacuation (23%), straining during bowel movements (19%), sensation of anorectal obstruction/blockage (16%), and infrequent stools (10%).⁶ Psychological symptoms such as depression, anxiety, and panic disorder also contribute to the diminished quality of life in patients with IBS.^{7,8} The economic impact of IBS can be substantial due to work absenteeism, presenteeism (ie, working while sick, often resulting in a loss in productivity), and decreased productivity.⁴

Comorbidities

Unfortunately, patients with IBS frequently have to cope with a variety of other health conditions as well. The IBS in America 2017 survey of 1337 people with an IBS diagnosis showed that 51% also suffer from allergies, 50% from anxiety or panic disorders, 47% from being overweight or obese, 40% from gastroesophageal reflux disease (GERD), 39% from arthritis, and 22% from hypertension.⁹

Analysis of the 2013 Truven Health MarketScan research database (n=19,653 each for IBS-D and matched controls) showed that one-quarter of patients with IBS-D suffer from GERD, while one-in-five suffer from anxiety, functional/chronic pain, depression, and/or malaise/fatigue.¹⁰

Barriers to care

An estimated 11% of people worldwide suffer from IBS, yet the diagnosis of IBS in the United States is often delayed, with one estimate indicating it may take an average of nearly 3 years from the onset of symptoms.¹¹ Another survey of 1094 individuals meeting criteria for IBS-D found that 43.1% had not received a formal diagnosis of IBS.⁵ One reason for this is that patients with IBS often initially ignore or self-manage their symptoms. According to the IBS in America 2017 sur-

vey, 53% tolerated the symptoms at first and went on with their life.⁹ Twenty-six percent thought the symptoms were not serious enough to seek medical care, while 43% tried to treat their symptoms with over-the-counter treatments. Twenty-nine percent weren't aware that their symptoms were the result of a medical condition.

The IBS in America 2017 survey also showed that half were relieved to receive a diagnosis for their symptoms highlighting the importance of educating patients to their condition. Unfortunately, one-third felt their health care provider was dismissive of their symptoms.⁹ At diagnosis, the majority of patients wish they had received education about: (1) how IBS relates to diet (71%); (2) symptoms of IBS (69%); (3) the effect of IBS on lifestyle (63%); (4) the impact of IBS on mental health (62%); and (5) different types of medication options and how they work (60%).

Additional barriers to care include patient misconceptions regarding normal bowel function and difficulty communicating with health care providers, including being afraid to misspeak, not using the right language, and embarrassment. Patients often have limited understanding of treatment goals and options, particularly related to treatment safety. Being able to afford treatment is also a common barrier, resulting in suboptimal adherence.

Half of the patients responding to the IBS in America 2017 survey were upset that there is no cure for IBS and nearly two-thirds were frustrated that they might never find a way to manage their symptoms. While nearly one-quarter of patients were satisfied with self-management of symptoms, nearly half were not satisfied with the care they receive from their health care provider.

Providers may not always inquire about bowel function and habits, and when they do, competing care agendas may result in less attention to the patient's gastrointestinal (GI) symptoms. Consequently, providers often underestimate the disease burden imposed on patients by IBS.¹² A recent analysis of over 200,000 patients with IBS found that there are wide geographic variations in IBS care.¹³

These barriers to care can be ameliorated through patient-provider communication and building a mutually respectful therapeutic relationship. A good patient-provider relationship fosters mutual understanding and helps the patient with IBS make sense of their symptoms, leading to an improved ability to self-manage IBS and maintain a better quality of life.¹⁴ Patients want more information about their condition so that they can understand and apply self-management techniques to treat their IBS symptoms.¹² Educational points that have been found to benefit most patients with IBS are listed in **TABLE 1**.¹² An empathetic approach is invaluable as well.

One approach to improve patient-provider communication and strengthen the therapeutic relationship is the technique of shared decision-making. The SHARE approach, recommended by the Agency for Healthcare Research and Quality, is a five-step process that includes exploring and comparing the benefits, harms, and risks of each option through meaningful dialogue about what matters most to the patient. A variety of tools and guides to implement the SHARE approach are available at: <https://www.ahrq.gov/professionals/education/curriculum-tools/shareddecisionmaking/tools/index.html>.

PATHOPHYSIOLOGY

The precise etiology of IBS remains unclear, but a combination of psychological factors and GI dysfunction appears to be central to its pathophysiology. These include changes in the gut microbiota, low-grade mucosal inflammation, epithelial dysfunction, genetic polymorphisms, and environmental factors such as diet and enteric infections.¹⁵ Identification of these factors and their interaction with the brain has resulted in the current concept that IBS is a disorder of gut-brain interactions.¹⁶

Increasing evidence implicates the GI microbiota as a key factor in the pathogenesis of IBS.^{17,18} Various studies have compared the gut microbiota in patients with IBS to healthy volunteers. No consistent alteration in specific microbes has been identified, likely due to the heterogeneous nature of IBS. A recent systematic review showed a decrease in *Clostridium*, *Faecalibacterium*, and *Bifidobacterium* species and an increase in *Enterobacteriaceae*, *Lactobacillus*, and *Bacteroides* species.¹⁹ Notably, the diversity of the gut microbiota was either decreased or not different in patients with IBS compared with controls.

Additional evidence supporting the importance of the gut microbiota in IBS symptoms is that a prior acute infectious gastroenteritis is the strongest risk factor for IBS. The prevalence of postinfectious IBS among those who experience infectious enteritis is thought to range from 4% to 36%,²⁰⁻²² although some experts believe it may be higher.¹⁵ Postinfectious IBS is thought to arise due to an interaction between central and peripheral factors; it is unknown if there are unique pathophysiologic mechanisms contributing to postinfectious IBS.¹⁵ The main risk factors include female sex, younger age, psychological factors (eg, anxiety, depression, somatization, neuroticism, negative illness beliefs) before or during the acute gastroenteritis, and severity of the acute episode. Evidence suggests that postinfectious IBS symptoms decrease over time and the prognosis may be better than for patients with IBS who do not have a preceding infection.¹⁵

The role of infectious gastroenteritis as a risk factor for IBS suggests that systemic inflammation in concert with an

TABLE 1 Educational points that benefit most patients with IBS

• IBS is a real GI condition; it is not 'in your head'.
• IBS can significantly affect one's quality of life.
• IBS is a chronic medical condition for most patients, although the symptoms can fluctuate over time.
• IBS does not cause cancer, colitis, or any other problems. It does not shorten your life.
• There are many things we can do to help you better manage your IBS symptoms.
• There is no 'magic pill' that can cure all IBS symptoms.
• For some people with IBS, stress can trigger symptoms or make them worse.
• We need to work together to help you manage your IBS.

Abbreviations: GI, gastrointestinal; IBS, irritable bowel syndrome.

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altered gut microbiome may lead to a cycle of chronic, low-grade, subclinical inflammation. In addition to mucosal inflammation, neuroinflammation may be involved via the gut-brain axis leading to altered neuroendocrine pathways and glucocorticoid receptor genes, resulting in an overall proinflammatory phenotype and dysregulated hypothalamic-pituitary-adrenal axis and serotonergic functioning.²³

PATIENT MANAGEMENT

Recently, Lacy et al proposed 7 pillars of quality care for patients with IBS that align with quality indicators described by The National Academy of Medicine (**TABLE 2**).²⁴ Noting that IBS is a highly prevalent, chronic disorder, they suggest that implementation of these quality metrics will help to ensure that all patients are evaluated fairly and similarly and provided with an adequate level of care. Moreover, they note the importance of quality metrics in determining reimbursement.

Diagnosis

The diagnosis of IBS can be confidently made based on a thoughtful history, physical examination, limited laboratory testing, and the use of the Rome IV criteria.^{17,24} Abdominal bloating and distension are often present, but neither is required for the diagnosis of IBS. Patients should be asked about their most troublesome symptom and possible warning signs or 'red flags,' such as presence of overt GI bleeding, nocturnal passage of stool, unintentional weight loss, age >45 years without prior colon cancer screening, and family history of IBD or colorectal cancer. If a red flag symptom is identified, further assessment is appropriate.

In the absence of red flags, limited testing is recom-

mended to include: (1) complete blood count to ensure the absence of anemia; (2) C-reactive protein and/or fecal calprotectin to lower the suspicion for IBD and to prevent indiscriminate use of colonoscopy; and (3) serologic testing to rule out celiac disease.^{17,25} In those without red flag symptoms, further testing does not increase the sensitivity of the diagnosis.^{26,27} A colonoscopy should be limited to patients with persistent diarrhea with suspected IBD, those who have failed empiric therapy, or age-appropriate patients with worrisome changes in bowel habits.²⁴ Consideration should be given to additional conditions that mimic IBS, such as lactose or fructose intolerance, small intestine bacterial overgrowth, microscopic colitis, and functional constipation or diarrhea.^{28,29} Stool studies are not routinely recommended; these should be performed based on the patient's history of travel, antibiotic use, and possible exposure. The presence of comorbidities that increase the likelihood of a functional GI disorder should be investigated as well. Examples include fibromyalgia, temporomandibular joint syndrome, migraine headaches, and interstitial cystitis.

Utilization of the Rome IV criteria (<https://theromefoundation.org/rome-iv/whats-new-for-rome-iv/>) is encouraged to facilitate making a positive diagnosis as opposed to a diagnosis of exclusion. Rome IV criteria require recurrent abdominal pain at least 1 day/week (on average) in the last 3 months associated with at least 2 of the following: (1) related to defecation; (2) associated with a change in stool frequency; and (3) associated with a change in form of stool. Symptom

onset should be at least 6 months prior to diagnosis. A key feature of the Rome IV criteria is that IBS subtype is based on the proportion of days per month with symptomatic bowel movements rather than measuring all days.

The Rome IV criteria are also useful to categorize IBS sub-type, ie, IBS-C, IBS-D, or IBS-M, based on the predominant symptom.²⁵ The estimated proportion of patients with IBS-D, IBS-C, and IBS-M is 40%, 35%, and 23%, respectively.³⁰ Women with IBS are more likely to experience abdominal pain and constipation-related symptoms, while men with IBS are more likely to experience diarrhea-related symptoms.³¹

Treatment

The treatment of patients with IBS-D can be approached based on symptom severity (**FIGURE**).¹⁷ For patients with severe IBS-D symptoms, the goal is to improve function and quality of life, rather than completely eliminating all symptoms. Nonpharmacologic therapy plays a role at all severity stages, while the importance of pharmacologic therapy increases with severity. A key principle of treatment is to focus on the IBS subtype and predominant symptom (**TABLE 2**).²⁴

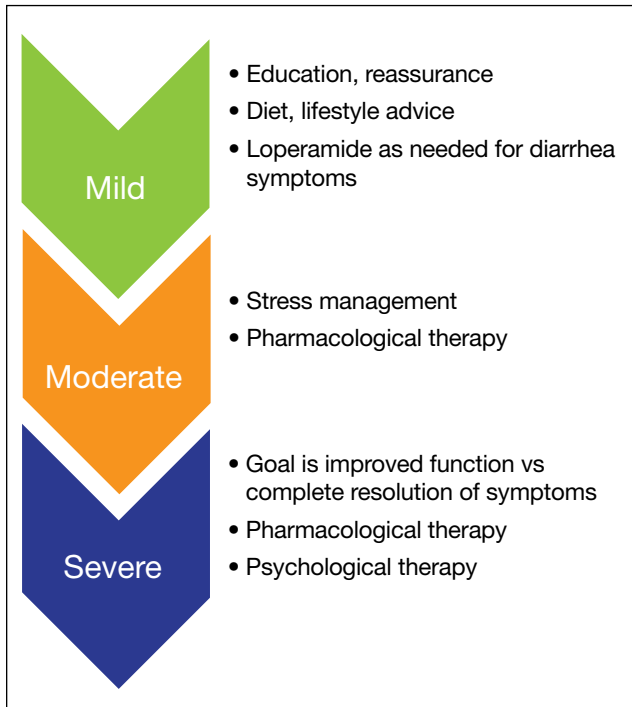
In 2018, the American College of Gastroenterology (ACG) updated their 2014 guidelines providing evidence-based recommendations regarding the nonpharmacologic and pharmacologic management of patients with IBS.³² For IBS-D, the 2018 review recommends several nonpharmacologic options for overall symptom improvement. These include exercise, soluble fiber, a low fermentable oligo-, di-, mono-saccharides

TABLE 2 Seven pillars of quality care in IBS

Positive diagnosis	<ul style="list-style-type: none"> • Make a positive diagnosis as soon as possible • Use Rome IV criteria to accurately categorize each patient based on bowel symptoms (IBS-C, IBS-D, IBS-M)
Limited testing	<ul style="list-style-type: none"> • Perform limited diagnostic testing at the first visit • CBC, CRP, and fecal calprotectin and celiac serologies, if clinically indicated
Limited colonoscopy	<ul style="list-style-type: none"> • Not required in all patients with suspected IBS symptoms • Perform in patients with suspected IBD, those with persistent symptoms of diarrhea who have failed standard therapy, and age-appropriate patients with a change in bowel habits or who require colorectal cancer screening
Patient education	<ul style="list-style-type: none"> • Counsel on the diagnosis of IBS; review treatment options and expectations; discuss fears and concerns about diagnosis and management
Treatment	<ul style="list-style-type: none"> • Initiate treatment at the initial visit or follow-up visit after limited diagnostic testing, based on guidelines, consensus statements, and large RCTs • Focus on the predominant symptom
Dietary consultation	<ul style="list-style-type: none"> • Request in those with persistent symptoms thought to be related, in part, to diet who have failed empiric therapy
Referral as needed	<ul style="list-style-type: none"> • Refer patients with persistent psychological distress, eg, anxiety, depression, somatization, catastrophization, affecting quality of life for appropriate evaluation and treatment

Abbreviations: CBC, complete blood count; CRP, C-reactive protein; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; IBS-M, irritable bowel syndrome with mixed symptoms of constipation and diarrhea; RCTs, randomized clinical trials.

Source: Lacy BE, Ford AC, Talley NJ. Quality of care and the irritable bowel syndrome: Is now the time to set standards? *Am J Gastroenterol*. 2018;113(2):167-169; https://journals.lww.com/ajg/Citation/2018/02000/Quality_of_Care_and_the_Irritable_Bowel_Syndrome_3.aspx. ©2018 by the American College of Gastroenterology.

FIGURE Severity-based treatment of IBS-D

Abbreviation: IBS-D, diarrhea-predominant irritable bowel syndrome.

and polyols (FODMAP) diet, and probiotics. Soluble fiber should be in the form of psyllium rather than wheat bran. Probiotics may help some patients, although the best dose and strain of probiotic are unknown. The ACG panel recommended against the use of a gluten-free or exclusion diet, as well as prebiotics and synbiotics, due to the lack of data.³² Psychological therapies such as cognitive behavioral therapy, relaxation therapy, hypnotherapy, and multicomponent psychological therapy are also recommended for overall symptom improvement.³²

Regarding pharmacotherapy options for IBS-D, alosetron, eluxadoline, rifaximin, some antidepressants, and antispasmodics are recommended for overall symptom improvement (**TABLE 3**).³² Alosetron is a selective serotonin antagonist that is recommended only for women with severe IBS-D who have failed standard therapy. Its use is limited due to the possibility of severe constipation and ischemic colitis. Eluxadoline is a mixed opioid agonist-antagonist that may be particularly useful to improve stool consistency. Eluxadoline should not be used in those with prior cholecystectomy or in patients who abuse alcohol or who have a history of pancreatitis, due to an increased risk of pancreatitis. Rifaximin is a nonabsorbable antibiotic that can help global IBS-D symptoms, especially bloating in some patients. Research has shown that rifaximin may cause modest changes in the gut microbiota, although these changes are not sustained. Tricyclic antidepressants improve IBS-D symptoms through both

TABLE 3 Therapies recommended for IBS-D

Intervention	Relative risk of remaining symptomatic vs placebo (95% CI)	Number needed to treat (95% CI)	Strength of recommendation	Level of evidence
Alosetron	.79 (.69-.90)	7.5 (5-16)	Weak	Low
Eluxadoline	.91 (.85-.97)	12.5 (8-33)	Weak	Moderate
Rifaximin	.86 (.81-.91)	10.5 (8-16)	Weak	Moderate
Tricyclic antidepressants	.65 (.55-.77)	4 (3.5-7)	Strong	High
Selective serotonin reuptake inhibitors	.68 (.51-.91)	5 (3-16.5)	Weak	Low
Antispasmodic, eg, dicyclomine	.65 (.45-.95)	4 (2-25)	Weak	Very low
Peppermint oil	.54 (.39-.76)	4 (3-6)	Weak	Low

Abbreviations: CI, confidence interval; IBS, irritable bowel syndrome.

Adapted with permission from Wolters Kluwer Health, Inc.: Ford AC, Moayyedi P, Chey WD, et al. American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome. *Am J Gastroenterol*. 2018;113(Suppl 2):1-18; <https://journals.lww.com/ajg/toc/2018/06002>. ©2018 by the American College of Gastroenterology.

central and visceral effects, and while pain-modifying effects are observed, their use may be limited by adverse events, such as dry mouth. The antispasmodics dicyclomine and peppermint oil may provide short-term improvement in overall symptoms. The use of enteric coated peppermint oil may reduce the occurrence of heartburn sometimes experienced with other peppermint oil preparations.

Dietary consultation may be considered for patients who have failed empiric therapy and have persistent symptoms thought to be related, in part, to diet. Sub-specialty referral may be considered for patients with persistent psychological distress, eg, anxiety, depression, somatization, or catastrophization, that affects quality of life.²⁴

SUMMARY

IBS is a common disorder that causes substantial patient morbidity; however, health care providers may underestimate the patient's disease burden. Greater understanding of the pathophysiology indicates that IBS is both a brain-gut and gut-brain disorder, with the gut microbiota playing a key role. The diagnosis of IBS is primarily based on the history and physical examination that includes fulfilment of the Rome IV criteria, supplemented by limited testing to rule out disorders that may mimic IBS. Treatment is individualized based on the patient's predominant symptom and concerns. Treatment usually begins with dietary modifications, increased exercise, and stress reduction. Evidence-based pharmacologic options for IBS-D include alosetron, eluxadoline, rifaximin, tricyclic antidepressants, diet, and smooth muscle antispasmodics, with the choice based on benefits, risks, and costs. ●

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