School of Pharmacy and Pharmaceutical Sciences
University at Buffalo The State University of New York

Drug Information Newsletter

Spring 2017

In this issue…

The University at Buffalo School of Pharmacy and Pharmaceutical Sciences (UB SPPS) Drug Information Newsletter is dedicated to providing timely information relevant to healthcare practitioners in New York. The newsletter supplies information on clinical practice guidelines, medication safety issues, new drug approvals/medications under development, medication shortages, and drug class reviews.

A Review of the 2017 American Diabetes Association Standards of Medical Care in Diabetes

Patrick McCabe, PharmD, MBA

The American Diabetes Association (ADA) publishes updates to the Standards of Care in Diabetes annually.[1] Other clinical practice guidelines, such as those published by the American Association of Clinical Endocrinologists (AACE), may differ in their treatment approach. However, for the general practitioner, the ADA guidelines can be a common source of treatment information. This article highlights the major changes in the latest version of the guideline, published in January 2017. Changes deemed relevant to most practice sites and of the greatest clinical significance will be described and organized in sections as outlined in the ADA guideline.

General Overview

In their 2017 guideline, the ADA emphasizes the importance of psychosocial care in the treatment of diabetes.[1] As such, the ADA addresses issues such as patient self-management and provider-patient communication, as well as diabetic complications, patient mental health, comorbidities, and life stage considerations.

Section 1: Promoting Health and Reducing Disparities in Populations

This section was renamed from “Strategies for Improving Care” in the 2016 guideline;[2] however, the purpose remains unchanged, with recommendations to address public health concerns including access to diabetes care.[1,2] The 2017 guideline places additional focus on improving outcomes and increasing provider awareness of diabetes health disparities

in at risk populations.[1] Recommendations include provider assessment of social issues including patient abilities to acquire food and housing, as well as financial barriers to treatment; these factors should be considered when developing a chronic care plan. A continued focus of this area is referral of patients, particularly those in underserved communities, to support resources, such as diabetes prevention programs (DPPs), diabetes self-management education and training (DSME/T) classes, or lay health coaches.

Section 2: Classification and Diagnosis of Diabetes

Several significant updates are present in this section.[1,2] The ADA asserts that the pathophysiology of diabetes is more developed in patients with type 1 vs. type 2 diabetes, and that studies evaluating first-degree relatives of patients with type 1 diabetes have led to a clearer understanding of the etiology.[1] Three stages have been identified; these are described in Table 1.

Table 1. Stages of type 1 diabetes.[1]

	Stage 1	Stage 2	Stage 3
Stage	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Clinical symptoms • Diabetes by standard criteria

The 2017 guideline also offers clarification on screening and diagnosis of diabetes.[1] One new recommendation is for the use of informal assessments or validated tools to screen for prediabetes and risk for future diabetes in asymptomatic adults. The ADA includes a risk tool as an easy option to use for screening. The ADA also suggests that screening for diabetes in dental practices, with referral to primary care, may be useful. Of note, the ADA maintains that community screening for diabetes outside of a healthcare setting is not recommended, due to lack of follow-up testing and care and potential issues in recruitment or targeting of patients at risk for diabetes.

Section 3: Comprehensive Medical Evaluation and Assessment of Comorbidities

This is a new section containing components of the previous section titled “Foundations of Care and Comprehensive Medical Evaluation.”[1,2] In this section, the ADA focuses on provider assessment of a patient’s comorbidities.[1] Their recommendations are shown in Table 2. The components of a comprehensive diabetes evaluation are also included in this section. The ADA addresses patient immunization status and reviews selected disease states in subsections. The list of comorbidities they review has been expanded from their previous guideline and now includes autoimmune diseases, human immunodeficiency virus, anxiety disorders, depression, disordered eating behavior, and serious mental illness.[1,2]

Table 2. ADA recommendations on comprehensive medical evaluation of patients with diabetes.[1]

Recommendation	Level of evidence[a]
Confirm diagnosis and classify diabetes	B
Detect complications and potential comorbidities	E
Review previous treatment and risk factor control	E
Begin patient engagement in forming care management plan	B
Develop a continuing care plan	B

[a]B=supportive evidence from well-conducted cohort studies or case-control studies; E=expert consensus or clinical experience.

Section 4: Lifestyle Management

"Lifestyle Management" is the remainder of the section previously entitled "Foundations of Care and Comprehensive Medical Evaluation," and concentrates on lifestyle recommendations for patients with diabetes.[1,2] Many of the recommendations from this section remain consistent with the previous version of the guideline, especially with regard to the recommendation for patient education in the form of DSME/T. However, there are some updates to their recommendations on physical activity.

All patients with diabetes who are physically able are advised to increase physical activity as much as possible.[1] The ADA recommends 150 minutes per week of moderate to vigorous physical activity for most adults. Previously, the ADA also recommended reducing sedentary time to <90 consecutive minutes.[2] In their 2017 update, the ADA recommends that prolonged sitting be interrupted every 30 minutes with short periods of physical activity.[1] Another new recommendation is for the addition of balance and flexibility training 2-3 times weekly for older adults. This is a light intensity activity which is beneficial both for the purpose of improving glycemic control as well as reducing risk of injury due to falls.

Section 6: Glycemic Targets

The most significant update regarding target blood glucose levels comes at the recommendation of the International Hypoglycaemia Study Group.[4] This group is a panel of experts which from organizations around the world, including the ADA and its European counterpart, the European Association for the Study of Diabetes; this group focuses on the prevention and treatment of low blood glucose. Traditionally, hypoglycemia was defined objectively as blood glucose levels ≤70 mg/dL. In the updated guideline, the ADA labels this threshold as a "glucose alert value," which should prompt treatment but not be alarming.[1] Instead, they state that clinically significant hypoglycemia is defined as blood glucose levels <54 mg/dL.

Section 7: Obesity Management for the Treatment of Type 2 Diabetes

Obesity is a major risk factor for the development of type 2 diabetes.[1] Per the ADA, management of obesity can delay the progression from prediabetes to diabetes, and weight loss in obese patients with diabetes may lead to better glycemic control, better insulin sensitivity, and reduction of cardiovascular risk factors. While many of the recommendations in this section remain the same compared to those in the previous guideline,[2] there are updated recommendations on bariatric surgery, which the ADA refers to as metabolic surgery.[1]

Per the ADA, there are accumulating data to suggest that metabolic surgeries can be more effective than traditional lifestyle and/or medical interventions in improving blood glucose control and complications, as well as long-term survival.[1] In a joint statement issued by international diabetes organizations,[5] including the ADA, several randomized controlled trials were identified, as well as a meta-analysis. Gloy et.al.[6] evaluated 11 randomized controlled trials comparing current bariatric surgery techniques to non-surgical treatment in patients with body mass index (BMI) ≥30 kg/m^2. They found that the individuals undergoing surgery had greater weight loss (mean difference -26 kg, 95% confidence interval [CI] -31 to -21) and higher remission rate of type 2 diabetes (relative risk [RR] 22.1, 95% CI 3.2 to 154.3) compared to those who received non-surgical treatment. Previously, the ADA recommended metabolic surgery for patients with BMI >35 kg/m^2; at present, the ADA expanded the eligibility criteria to include patients with BMI ≥30 kg/m^2 whose blood glucose is not adequately controlled with optimal medication therapy. This may prove to be a significant change in future therapy.

Section 8: Pharmacological Approaches to Glycemic Control

This section, previously titled "Approaches to Glycemic Treatment," has been updated with several changes, including additional monitoring parameters for patients on metformin (periodic measurement of B12 levels with supplementation as needed), a discussion of newly available biosimilar insulins, a modified algorithm for the use of combination injectable therapy, and tables comparing the median costs of antidiabetic agents.[1,2] Also clinically significant is the recommendation

to consider use of empagliflozin or liraglutide in patients with established cardiovascular disease to reduce the risk of mortality.[1]

The ADA refers to 2 clinical trials evaluating the cardiovascular outcomes of patients taking these agents: EMPA-REG OUTCOME and LEADER.[1,7,8] EMPA-REG OUTCOME[7] is a randomized, double-blind trial in which investigators evaluated the effect of empagliflozin compared to placebo, added to standard care, in patients with type 2 diabetes and established cardiovascular disease. The primary outcome was a composite of non-fatal myocardial infarction (MI), stroke, and cardiovascular death. Over 7,000 patients were included in their analysis, and the median follow-up period was 3.1 years. Empagliflozin, compared to placebo, was associated with a lower rate of cardiovascular outcomes (10.5% vs. 12.1%; hazard ratio [HR] 0.86, 95% CI 0.74 to 0.99). LEADER[8] is another randomized, double-blind trial, conducted to evaluate the cardiovascular effect of adding liraglutide vs. placecbo to standard care in patients with type 2 diabetes. The primary outcome in this study was also a composite of cardiovascular death, nonfatal MI, and nonfatal stroke. Over 9,000 patients were included with a mean follow-up period of 3.8 years. There was a lower rate of cardiovascular outcomes in patients using liraglutide versus patients using placebo (13.0% vs 14.9%; HR 0.87, 95% CI 0.78 to 0.97). These trials led to the guideline consideration of these agents for special use in patients with established cardiovascular disease.

Section 9: Cardiovascular Disease and Risk Management

In addition to a discussion on the potential benefits of empagliflozin and liraglutide in patients with diabetes and cardiovascular disease, the ADA amended their recommendations on treatment of hypertension.[1] Previously, the ADA recommended use of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB).[2] In their 2017 guideline, the ADA states that patients with high blood pressure without albuminuria may be treated with any of the 4 classes of blood pressure medications (ACE inhibitors, ARBs, thiazide-like diuretics, or dihydropyridine calcium channel blockers).[1] In patients with albuminuria, the ADA recommends an ACE inhibitor or ARB, as these agents are associated with lower risk of kidney damage.

Section 10: Microvascular Complications and Foot Care

Microvascular complications of diabetes include retinopathy, nephropathy, and neuropathy.[1] The most significant update to this section is regarding diabetic neuropathy. In their 2016 guideline, the ADA recommended that steps be taken to optimize blood glucose control and to treat the pain; however, while agents for treatment of neuropathic pain were mentioned, no agents were strongly recommended.[2] In the new guideline, however, pregabalin or duloxetine are recommended as initial agents for the treatment of neuropathic pain.[1] The ADA focuses specifically on diabetic neuropathy in a recently published position statement.[9] In this statement, the ADA asserts that gabapentin may be an additional option for initial treatment and that tricyclic antidepressants may also be an effective option. However, the ADA recommends against the use of opioid agents given the risk of addiction to these medications.

Conclusions

The most recent edition of the ADA Standards of Care may be a valuable tool in the treatment of patients with diabetes. The updates to these guidelines reviewed above showcase how the guidelines are transitioning to holistic treatment approaches evaluating the whole patient.[1] The ADA asserts that their guidelines will be updated annually as new evidence emerges.

References

1. American Diabetes Association. Standards of medical care in diabetes-2017. *Diabetes Care*. 2017;40(Suppl 1):S1-S135.
2. American Diabetes Association. Standards of medical care in diabetes-2016. *Diabetes Care*. 2016;39(Suppl 1):S1-S112.
3. Skyler JS, Bakris GL, Bonifacio E, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. *Diabetes*. 2017;66(2):241-255.

4. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2017;40(1):155–157.
5. Rubino F, Nathan DM, Eckel RH, et al. Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations. *Diabetes Care*. 2016;39(6):861-877.
6. Gloy VL, Briel M, Bhatt DL, et.al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2013;347:f5934.
7. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117–2128
8. Marso SP, Daniels GH, Brown-Frandsen K,et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311–322.
9. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40(1):136-154.

Epclusa® Drug Monograph Review

Emily Leppien, PharmD

Introduction

Sofosbuvir-velpatasvir (Epclusa®) was approved by the Food and Drug Administration (FDA) in June 2016 for the treatment of chronic hepatitis C virus (HCV) infection in adult patients with genotype 1, 2, 3, 4, 5 and 6 without cirrhosis or with compensated cirrhosis (Child-Pugh A), or in combination with ribavirin (RBV) in adults with decompensated cirrhosis (Child-Pugh B or C).[1] The confirmed efficacy of sofosbuvir-velpatasvir is particularly beneficial for patients with HCV genotype 2 and 3, as prior to its approval, there was a lack of pharmacologic treatment options for these HCV genotypes. Though not specifically addressed in the product labeling, the efficacy of sofosbuvir-velpatasvir in patients with human immunodeficiency virus (HIV)-1 and HCV coinfection is also under investigation.[2]

Sofosbuvir and velpatasvir are both direct-acting antiviral (DAA) agents.[1] Sofosbuvir is a nucleotide prodrug that undergoes hepatic intracellular metabolism to form an active analog (GS-461203). This active compound is incorporated into HCV ribonucleic acid (RNA) by nonstructural protein 5B (NS5B) polymerase to act as a chain terminator, preventing further viral replication. Velpatasvir inhibits the HCV nonstructural protein 5A (NS5A), which is vital for viral replication.

Researchers in the Netherlands have found, through an indirect meta-analysis comparison, sofosbuvir-velpatasvir is the most effective regimen for the treatment of HCV in adult patients with genotype 3, compared to its predecessor DAA regimens.[3] Evaluation of treatment options in genotype 3 was specifically investigated, as prior to the approval of sofosbuvir-velpatasvir, there were limited treatment options FDA approved for the treatment of this genotype. It is likely that head-to-head trials directly comparing sofosbuvir-velpatasvir to other DAA agents will be conducted in the near future, especially since Harvoni® (ledipasvir-sofosbuvir) had the highest total cost in Medicaid drug spending in 2015.[4]

Efficacy

The efficacy of sofosbuvir-velpatasvir was investigated in 4 phase III clinical trials (ASTRAL-1, ASTRAL-2, ASTRAL-3 and ASTRAL-4).[5-7] Selected characteristics of the methods employed in these studies are outlined in Table 1. In ASTRAL-1 and ASTRAL-4, randomization was stratified by HCV genotype.[5,7] In all 4 trials, sofosbuvir-velpatasvir was administered in a fixed-dose combination of 400 mg and 100 mg, respectively, once daily.[5-7] Ribavirin was administered in doses determined by body weight (<75kg: 1000 mg daily; ≥75kg: 1200 mg daily).[6,7] The primary endpoint for all 4

trials was sustained virologic response (SVR), defined as HCV RNA level ≤15 IU/mL, measured at week 12 post-treatment.[5-7]

Table 1. Selected characteristics of phase III trials of sofosbuvir-velpatasvir.[1,5-7]

Trial	Design and Duration	Population[a]	Treatment Groups[b]
ASTRAL-1	R, DB, PC 12 weeks[c]	Genotype 1, 2, 4, 5 or 6 Treatment naïve and experienced, with cirrhosis, including compensated cirrhosis	Sofosbuvir-velpatasvir (n=624) Placebo (n=116)
ASTRAL-2	R, OL 12 weeks[c]	Genotype 2 Treatment naïve and experienced, with cirrhosis, including compensated cirrhosis	Sofosbuvir-velpatasvir (n=134) Sofosbuvir + ribavirin (n=132)
ASTRAL-3	R, OL 24 weeks	Genotype 3 Treatment naïve and experienced, with cirrhosis, including compensated cirrhosis	Sofosbuvir-velpatasvir x 12 weeks (n=277) Sofosbuvir + ribavirin x 24 weeks (n=275)
ASTRAL-4	R, OL 24 weeks	Genotype 1, 2, 3, 4, 5, 6 Treatment naïve and experienced, with decompensated cirrhosis	Sofosbuvir-velpatasvir x 12 weeks (n=90) Sofosbuvir-velpatasvir + ribavirin x 12 weeks (n=87) Sofosbuvir-velpatasvir x 24 weeks (n=90)

DB=double-blind, OL=open-label, PC=placebo-controlled, R=randomized

[a]Compensated cirrhosis classified as Child-Pugh class A; decompensated cirrhosis classified as Child-Pugh class B.

[b]Study treatment was administered as a fixed-dose combination containing 400 mg of sofosbuvir and 100 mg of velpatasvir, administered once daily.

[c]Treatment duration was the same for both groups.

SVR rates at 12 weeks post-treatment, for all patients, by genotype, from ASTRAL trials 1-4 are outlined in Table 2. In ASTRAL-1, the rate of SVR among patients who received sofosbuvir-velpatasvir therapy was 99% overall, showing statistical significance when compared to the prespecified goal of 85% ($p<0.001$).[5] No patients in the placebo group achieved SVR at 12 weeks. In ASTRAL-2 and ASTRAL-3, the rate of SVR among adult patients treated with sofosbuvir-velpatasvir was superior to the rate achieved with sofosbuvir plus ribavirin after 12 weeks (95% confidence interval [CI] 0.2-10.3, $p=0.02$) or 24 weeks (95% CI 9.6-20, $p<0.001$), respectively.[6]

Table 2. SVR rates for all patients, by genotype, in ASTRAL 1-4.[5-7]

Trial	Treatment	SVR rates at 12 weeks post-treatment, by genotype							
		1a	1b	2	3	4	5	6	Any
1	**SOF-VEL x 12 wks**	**98% (206/210)**	**99% (117/118)**	**100% (104/104)**	**N/A**	**100% (116/116)**	**97% (34/35)**	**100% (41/41)**	**99% (618/624)**
	Placebo	0% (0/116)							
2	**SOF-VEL x 12 wks**	N/A	N/A	99% (133/134)	N/A	N/A	N/A	N/A	N/A
	SOF + RBV x 12 wks			94% (124/132)					
3	**SOF-VEL x 12 wks**	N/A	N/A	N/A	95% (264/277)	N/A	N/A	N/A	N/A
	SOF + RBV x 24 wks				80% (221/275)				

Trial	Treatment	SVR rates at 12 weeks post-treatment, by genotype							
		1a	1b	2	3	4	5	6	Any
4	**SOF-VEL x 12 wks**	88% (44/50)	89% (16/18)	100% (4/4)	50% (7/14)	100% (4/4)	N/A	N/A	**83% (75/90)**
	SOF-VEL + RBV x 12 wks	94% (51/54)	100% (14/14)	100% (4/4)	85% (11/13)	100% (2/2)	N/A	N/A	**94% (82/87)**
	SOF-VEL x 24 wks	93% (51/55)	88% (14/16)	75% (3/4)	50% (6/12)	100% (2/2)	N/A	100% (1/1)	**86% (77/90)**

N/A=not applicable; RBV=ribavirin; SOF=sofosbuvir; SVR=sustained virologic response; VEL=velpatasvir

SVR rates at 12 weeks post-treatment, in patients with compensated cirrhosis are outlined in Table 3. In ASTRAL-1, 142 patients had compensated cirrhosis, with 121 patients in the sofosbuvir-velpatasvir treatment arm, while ASTRAL-2 included 38 patients with compensated cirrhosis, 19 of which were included in the sofosbuvir-velpatasvir treatment arm.[5,6] ASTRAL-3 included 163 patients with compensated cirrhosis, 80 of which were included in the sofosbuvir-velpatasvir treatment arm.[6] Patients with HCV genotype 1, 2, 4, 5 or 6 and compensated cirrhosis treated with sofosbuvir-velpatasvir had significantly higher SVR rates over placebo.[5] Patients with HCV genotype 3 and compensated cirrhosis treated with sofosbuvir-velpatasvir had significantly higher SVR rates over sofosbuvir plus ribavirin.[6]

Patients with decompensated cirrhosis, defined as Child-Pugh class B or C, were included in ASTRAL-4.[7] SVR rates for these patients, by genotype, are outlined in Table 3. All 3 treatment groups demonstrated statistically significant SVR rates 12 weeks post-treatment ($p<0.001$). Among patients with genotype 3, the treatment groups without ribavirin had lower SVR rates compared to the sofosbuvir-velpatasvir plus ribavirin group. However, post-hoc analyses did not find statistically significant differences in rates of SVR among the treatment groups.

Table 3. SVR rates for patients with cirrhosis, by genotype, in ASTRAL 1-4.[5-7]

Trial	Treatment	SVR rates at 12 weeks post-treatment, by genotype, in subjects with cirrhosis							
		1a	1b	2	3	4	5	6	Any
Compensated Cirrhosis									
1	**SOF-VEL x 12 wks**	100% (49/49)	96% (23/24)	100% (10/10)	N/A	100% (27/27)	100% (5/5)	100% (6/6)	**99% (120/121)**
	Placebo	0% (0/21)							
2	**SOF-VEL x 12 wks**	N/A	N/A	100% (19/19)	N/A	N/A	N/A	N/A	**N/A**
	SOF + RBV x 12 wks			95% (18/19)					
3	**SOF-VEL x 12 wks**	N/A	N/A	N/A	91% (73/80)	N/A	N/A	N/A	**N/A**
	SOF + RBV x 24 wks				66% (55/83)				
Decompensated Cirrhosis									
4	**SOF-VEL x 12 wks**	88% (44/50)	89% (16/18)	100% (4/4)	50% (7/14)	100% (4/4)	N/A	N/A	**83% (75/90)**
	SOF-VEL + RBV x 12 wks	94% (51/54)	100% (14/14)	100% (4/4)	85% (11/13)	100% (2/2)		N/A	**94% (82/87)**
	SOF-VEL x 24 wks	93% (51/55)	88% (14/16)	75% (3/4)	50% (6/12)	100% (2/2)		100% (1/1)	**86% (77/90)**

N/A=not applicable; RBV=ribavirin; SOF=sofosbuvir; SVR=sustained virologic response; VEL=velpatasvir

SVR rates at 12 weeks post-treatment for treatment-naïve versus treatment-experienced patients are outlined in Table 4. In ASTRAL-1, ASTRAL-2 and ASTRAL-3, 32%, 14% and 26% of patients, respectively, treated with sofosbuvir-velpatasvir received prior HCV treatment.[5,6] ASTRAL-4 did not include SVR rates separated by treatment-naïve versus experienced patients.[7] All previously treated patients in ASTRAL-1 received interferon-based therapy.[5] SVR rates among treatment-naïve and experienced patients were similar when compared by genotype.[5,6]

Table 4. SVR rates for treatment-naïve and treatment experienced patients in ASTRAL 1-3.[5,6]

Trial	Treatment	SVR rates at 12 weeks post-treatment by genotype						
		1a	1b	2	3	4	5	6
Treatment-naïve								
1	**SOF-VEL x 12 wks**	**98% (128/132)**	**100% (86/86)**	**100% (79/79)**	**N/A**	**100% (64/64)**	**96% (23/24)**	**100% (38/38)**
2	**SOF-VEL x 12 wks**	N/A	N/A	**100% (114/115)**	N/A	N/A	N/A	N/A
	SOF + RBV x 12 wks			96% (106/111)				
3	**SOF-VEL x 12 wks**	N/A	N/A	N/A	**97% (200/206)**	N/A	N/A	N/A
	SOF + RBV x 24 wks				86% (176/204)			
Treatment-experienced								
1	**SOF-VEL x 12 wks**	**100% (78/78)**	**97% (31/32)**	**100% (25/25)**	**N/A**	**100% (52/52)**	**100% (11/11)**	**100% (3/3)**
2	**SOF-VEL x 12 wks**	N/A	N/A	**100% (19/19)**	N/A	N/A	N/A	N/A
	SOF + RBV x 12 wks			85% (17/20)				
3	**SOF-VEL x 12 wks**	N/A	N/A	N/A	**90% (64/71)**	N/A	N/A	N/A
	SOF + RBV x 24 wks				63% (45/71)			

N/A=not applicable; RBV=ribavirin; SOF=sofosbuvir; SVR=sustained virologic response; VEL=velpatasvir

Once-daily sofosbuvir-velpatasvir for 12 weeks resulted in high rates of SVR among both previously treated and untreated patients infected with HCV genotype 1, 2, 4, 5 and 6.[5] Sofosbuvir-velpatasvir resulted in SVR rates that were superior to those of alternative, standard treatment regimens among both treatment-naïve and experienced patients infected with HCV genotype 2 and 3, including those with compensated cirrhosis.[6] SVR rates in patients treated with sofosbuvir-velpatasvir were highest among treatment-naïve patients without cirrhosis or with compensated cirrhosis (Child-Pugh A). In patients with decompensated cirrhosis (Child-Pugh B or C), treatment with sofosbuvir–velpatasvir for 24 weeks or in combination with ribavirin for 12 weeks resulted in high rates of SVR, with sofosbuvir–velpatasvir plus ribavirin for 12 weeks being the regimen of choice per the manufacturer.[1,7]

Safety

Contraindications: Sofosbuvir-velpatasvir is contraindicated in patients with a known hypersensitivity reaction to either sofosbuvir or velpatasvir.[1] In combination with ribavirin, this regimen is contraindicated in patients for whom ribavirin is

contraindicated, including women who are pregnant, men whose female partners are pregnant, in combination with didanosine, and in patients with hemoglobinopathies (i.e. sickle-cell anemia), autoimmune hepatitis, and creatinine clearance <50 mL/min.[8]

Warnings/precautions: Serious symptomatic bradycardia has been reported in patients receiving amiodarone and sofosbuvir in combination with another HCV DAA.[1] Concomitant use of sofosbuvir-velpatasvir and amiodarone is not recommended. In October 2016, the FDA issued a drug safety communication regarding the risk of hepatitis B reactivation with DAAs, including sofosbuvir-velpatasvir, and, as a result, boxed warnings will be added to DAA drug labels.[9]

Adverse reactions: In ASTRAL-1, ASTRAL-2, and ASTRAL-3, the most common adverse reactions in patients without cirrhosis or with compensated cirrhosis treated for 12 weeks were headache (22%) and fatigue (15%).[1,5,6] Only 0.2% of patients in these studies permanently discontinued treatment as a result of adverse effects. Additional adverse effects reported in ASTRAL-1 include nausea (9%), asthenia (5%) and insomnia (5%); the incidences were similar across all trials.[1,5-7] Most adverse events (79%) were of mild severity.[1] In patients with decompensated cirrhosis, also receiving ribavirin, ASTRAL-4 reported the most common adverse effects to be fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%) and diarrhea (10%).[1,7] Almost all of these effects (98%) were of mild-moderate severity.[1] Of note, irritability (>5%) was observed in the treatment arm of ASTRAL-3.[1,6]

Drug interactions: Sofosbuvir-velpatasvir is primarily metabolized by p-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and cytochrome P450 (CYP) 2B6, 2C8 and 3A4.[1] Therefore, moderate to strong inducers of P-gp, CYP2B6, CYP2C8 and CYP3A4 may decrease plasma concentrations of either sofosbuvir or velpatasvir. The manufacturer recommends avoiding the use of these agents with sofosbuvir-velpatasvir as optimal doses or dosage-adjustments to address the interactions are not known. Sofosbuvir-velpatasvir may be used concomitantly with P-gp, BCRP, and CYP inhibitors. On the other hand, velpatasvir is an inhibitor of P-gp, BCRP, and organic anion-transporting polypeptide (OATP) 1B1, 1B3 and 2B1. Therefore, coadministration of sofosbuvir-velpatasvir with P-gp, BCRP, and OATP substrates is cautioned, as their concentrations may increase.

Special populations: Safety and efficacy of sofosbuvir-velpatasvir have not been established in patients with severe renal impairment undergoing hemodialysis.[1] Currently, the manufacturer does not provide recommendations on dosage of sofosbuvir-velpatasvir in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73m^2) and end-stage renal disease. No dose adjustment recommendations for sofosbuvir-velpatasvir are provided for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C); however, monitoring is recommended in patients with decompensated cirrhosis.

Dosage and administration

Sofosbuvir-velpatasvir is supplied as a fixed-dose combination tablet containing 400 mg of sofosbuvir and 100 mg of velpatasvir.[1] The manufacturer recommends 1 tablet daily, with or without food. In patients without cirrhosis or with compensated cirrhosis, the manufacturer recommends administration of sofosbuvir-velpatasvir alone for 12 weeks. In patients with decompensated cirrhosis (Child-Pugh B or C), administration of sofosbuvir-velpatasvir in combination with ribavirin for 12 weeks is recommended. Ribavirin should be dosed by weight: 1000 mg/day in patients weighing <75kg and 1200 mg/day in patients weighing ≥75 kg.[8]

Place in therapy

The efficacy of sofosbuvir-velpatasvir in the treatment of HCV genotype 1-6 has been demonstrated in the aforementioned ASTRAL trials.[5-7] Unfortunately, the lack of head-to-head trials investigating sofosbuvir-velpatasvir and other DAAs precludes conclusions about its comparative efficacy. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have issued web-based guidance on the testing, management, and treatment of HCV, which were updated following the approval of sofosbuvir-velpatasvir.[10] The AASLD and IDSA include sofosbuvir-velpatasvir in their recommendations for the treatment of all HCV genotypes with a Class I Level A evidence rating (Table 5 and Table 6). For treatment-experienced patients, the recommended regimens are dependent upon previously attempted therapy. These guidelines state the choice of regimen should be based upon patient-specific factors, such as drug-drug interactions.

Table 5. Recommended treatment regimens for all HCV genotypes.[10]

Recommended Treatment Regimens per Genotype in Treatment-Naïve Patients	
Genotype 1a	
Without cirrhosis	Elbasvir 50 mg/grazoprevir 100 mg daily for 12 weeks (IA) Ledipasvir 90 mg/sofosbuvir 400 mg daily for 12 weeks (IA) Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily plus dasabuvir 250 mg twice daily with weight-based ribavirin for 12 weeks (IA) Simeprevir 150 mg plus sofosbuvir 400 mg daily for 12 weeks (IA) **Sofosbuvir 400 mg/velpatasvir 100 mg daily for 12 weeks (IA)** Daclatasvir 60 mg plus sofosbuvir 400 mg daily for 12 weeks (IB)
Compensated cirrhosis	Elbasvir 50 mg/grazoprevir 100 mg daily for 12 weeks (IA) Ledipasvir 90 mg/sofosbuvir 400 mg daily for 12 weeks (IA) **Sofosbuvir 400 mg/velpatasvir daily 100 mg for 12 weeks (IA)**
Genotype 1b	
Without cirrhosis	Elbasvir 50 mg/grazoprevir 100 mg daily for 12 weeks (IA) Ledipasvir 90 mg/sofosbuvir 400 mg daily for 12 weeks (IA) Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily plus dasabuvir 250 mg twice daily for 12 weeks (IA) Simeprevir 150 mg plus sofosbuvir 400 mg daily for 12 weeks (IA) **Sofosbuvir 400 mg/velpatasvir 100 mg daily for 12 weeks (IA)** Daclatasvir 60 mg plus sofosbuvir 400 mg daily for 12 weeks (IB)

Recommended Treatment Regimens per Genotype in Treatment-Naïve Patients	
Compensated cirrhosis	Elbasvir 50 mg/grazoprevir 100 mg daily for 12 weeks (IA) Ledipasvir 90 mg/sofosbuvir 400 mg daily for 12 weeks (IA) Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily plus dasabuvir 250 mg twice daily for 12 weeks (IA) **Sofosbuvir 400 mg/velpatasvir 100 mg daily for 12 weeks (IA)**
Genotype 2	
With/without compensated cirrhosis	**Sofosbuvir 400 mg/velpatasvir 100 mg daily for 12 weeks (IA)**
Genotype 3	
Without cirrhosis	Daclatasvir 60 mg plus sofosbuvir 400 mg daily for 12 weeks (IA) **Sofosbuvir 400 mg/velpatasvir 100 mg daily for 12 weeks (IA)**
Compensated cirrhosis	**Sofosbuvir 400 mg/velpatasvir 100 mg daily for 12 weeks (IA)** Daclatasvir 60 mg plus sofosbuvir 400 mg daily for 24 weeks with or without weight-based ribavirin (IIa-B)
Genotype 4	
With/without compensated cirrhosis	Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg daily and weight-based ribavirin for 12 weeks (IA) **Sofosbuvir 400 mg/velpatasvir 100 mg daily for 12 weeks (IA)** Elbasvir 50 mg/grazoprevir 100 mg daily for 12 weeks (IIa-B) Ledipasvir 90 mg/sofosbuvir 400 mg daily for 12 weeks (IIa-B)
Genotypes 5 and 6	
With/without compensated cirrhosis	**Sofosbuvir 400 mg/velpatasvir 100 mg daily for 12 weeks (IA)** Ledipasvir 90 mg/sofosbuvir 400 mg daily for 12 weeks (IIa-B)

Class I = Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective; Class II = Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment; Class IIa = Weight of evidence and/or opinion is in favor of usefulness and efficacy; Class IIb = Usefulness and efficacy are less established by evidence and/or opinion; Level A = Data derived from multiple randomized clinical trials, meta-analyses, or equivalent; Level B = Data derived from a single randomized trial, nonrandomized studies, or equivalent; Level C = Consensus opinion of experts, case studies, or standard of care.[10]

Table 6. Recommended HCV treatment regimens for patients with decompensated cirrhosis.[10]

Previous Treatment or Eligibility	*Recommended Treatment Regimens for Decompensated Cirrhosis per Genotype*
Genotypes 1 and 4	
Not specified	Ledipasvir 90 mg/sofosbuvir 400 mg with ribavirin 600 mg daily for 12 weeks (IA) **Sofosbuvir 400 mg/velpatasvir 100 mg with weight-based ribavirin daily for 12 weeks (IA)** Daclatasvir 60 mg + sofosbuvir 400 mg with ribavirin 600mg daily for 12 weeks (IB)
Ribavirin-ineligible	**Sofosbuvir 400 mg/velpatasvir 100 mg daily for 24 weeks (IA)** Daclatasvir 60 mg plus sofosbuvir 400 mg daily for 24 weeks (IIC) Ledipasvir 90 mg/sofosbuvir 400 mg daily for 24 weeks (IIC)
Sofosbuvir-based treatment	Ledipasvir 90 mg/sofosbuvir 400 mg with ribavirin 600 mg for 24 weeks (IIC) **Sofosbuvir 400 mg/velpatasvir 100 mg with weight-based ribavirin daily for 24 weeks (IIC)**
Genotypes 2 and 3	
Not specified	**Sofosbuvir 400 mg/velpatasvir 100 mg with weight-based ribavirin daily for 12 weeks (IA)** Daclatasvir 60 mg + sofosbuvir 400 mg with ribavirin 600mg daily for 12 weeks (IIB**)**

Class I = Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective; Class II = Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment; Class IIa = Weight of evidence and/or opinion is in favor of usefulness and efficacy; Class IIb = Usefulness and efficacy are less established by evidence and/or opinion; Level A = Data derived from multiple randomized clinical trials, meta-analyses, or equivalent; Level B = Data derived from a single randomized trial, nonrandomized studies, or equivalent; Level C = Consensus opinion of experts, case studies, or standard of care.[10]

Conclusions

Sofosbuvir-velpatasvir is a newly-approved DAA product for the treatment of chronic HCV in adult patients with genotype 1, 2, 3, 4, 5 or 6 with or without compensated cirrhosis, or in combination with ribavirin for patients with decompensated cirrhosis.[1] Four phase III clinical trials have demonstrated efficacy of once-daily sofosbuvir-velpatasvir in all HCV genotypes;[5-7] however, its efficacy in genotypes 2 and 3 are particularly significant, considering prior to its approval there was a lack of pharmacologic options to treat these genotypes. Sofosbuvir-velpatasvir demonstrated a favorable side effect profile compared to prior treatment regimen options, including interferon-based therapy. Rapid inclusion in HCV treatment guidelines as a first-line treatment option for all patient populations is significant, as once-daily sofosbuvir-velpatasvir resulted in high rates of SVR among both treatment-naïve and experienced patients infected with HCV genotype 1, 2, 3, 4, 5 or 6, including those with compensated and decompensated cirrhosis.

References

1. Epclusa® [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; 2016.
2. ClinicalTrials.gov. Efficacy and safety of sofosbuvir/velpatasvir fixed dose combination for 12 weeks in adults with chronic hepatitis C virus (HCV) and human immunodeficiency virus (HIV)-1 coinfection. https://clinicaltrials.gov/ct2/results?term=velpatasvir+HIV&Search=Search. Accessed December 23, 2016.
3. Berden FA, Aaldering BR, Groenwould H, Inthout J, Kievit W, Drenth JP. Identification of the best direct-acting antiviral regimen for patients with hepatitis C virus genotype 3 infection: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol*. 2017; 15(3):349-359.
4. Centers for Medicare and Medicaid Services (CMS). Medicaid drug spending dashboard 2015. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Dashboard/2015-Medicaid-Drug-Spending/2015-Medicaid-Drug-Spending.html. Accessed December 28, 2016.
5. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med.* 2015; 373(27): 2599-2607.
6. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med.* 2015; 373(27):2608-2617.
7. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. *N Engl J Med*. 2015; 373(27):2618-2628.
8. Ribavirin [prescribing information]. Whitehouse Station, NJ: Merck and Co., Inc.; 2016.
9. FDA Drug Safety Communication. FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C. October 4, 2016. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM523499.pdf. Accessed February 17, 2017.
10. AASLD-IDSA HCV Guidance Panel. Recommendations for testing, managing, and treating adults infected with hepatitis C virus. http://www.hcvguidelines.org. Accessed January 19, 2017.

Dementia Risk Amongst Patients Taking Proton Pump Inhibitors

Anthony Chiappelli, PharmD

Introduction

Proton pump inhibitors (PPIs) are drugs approved by the Food and Drug Administration (FDA) for various uses; these include treatment of gastrointestinal (GI) disorders including gastric and duodenal ulcer disease, *Helicobacter.pylori* eradication, heartburn, and gastroesophageal reflux disease (GERD).[1-3] PPIs irreversibly bind to hydrogen/potassium ATPase enzymes (proton pumps) on gastric parietal cells, inhibiting the release of free hydrogen ions.[2,3] This leads to a decrease in gastric acid and an increase in gastric pH, which may facilitate GI healing. Medications in the PPI class include omeprazole (Prilosec®), esomeprazole (Nexium®), lansoprazole (Prevacid®), rabeprazole (Aciphex®), pantoprazole (Protonix®), and dexlansoprazole (Dexilant®).[4] All of these drugs are available by prescription; esomeprazole, lansoprazole, and omeprazole are also available, at lower doses, over-the-counter.

According to Kantor et al, the prevalence of prescription PPI use in the United States increased from 3.9% in 1999-2000 to 7.8% in 2011-2012.[5] Rotman and Bishop reviewed data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey and reported that the prevalence of visits in which PPIs were used had increased from 4.0% of visits in 2002 to 9.2% in 2009.[6] Among the visits by patients on PPIs in 2009, 62.9% had no documented GI complaints or indications for PPIs. This is concerning, as overuse or unnecessary use of PPIs may result in increased risk for PPI-related adverse effects.

PPI use has been linked to an increased risk for infections, bone fractures, drug interactions, and nutritional deficiencies.[1] Recently, evidence has emerged suggesting that PPIs may be associated with an increased risk of dementia,[7] although the FDA has not yet recommended any changes to drug labeling of any PPIs. Dementia is a condition characterized by substantial impairment in 1 or more cognitive domains: complex attention, executive functioning, learning and memory,

language, perceptuomotor functioning, and social cognition.[8] The American Psychiatric Association notes that there are several risk factors for dementia, including age, female gender, and cardiovascular disease. Dementia is associated with a poor prognosis and prominent memory loss, with an estimated mean duration of survival after diagnosis of 10 years. Prominent memory loss causes significant difficulties relatively early in the course and progresses gradually with disease course ranging from mild to moderate with associated features at each stage. Associated symptoms progress from depression and/or apathy with mild psychotic features, irritability, agitation, and combativeness. Gait disturbance, dysphagia, incontinence, myoclonus, and seizures may also be observed.

Association of PPIs with dementia

PPIs are generally regarded as safe medications. However, recent data suggest that use of PPIs could be a risk factor for dementia and cognitive decline.[8] The evidence linking PPIs and dementia is conflicting. From a search of the literature, a meta-analysis was identified in which investigators sought to determine the risk of dementia with PPI use.[7] They included data from 4 observational studies reporting the risk of dementia among PPI users compared to non-users. Combining the data, they found a small, non-statistically significant increase in risk of dementia associated with PPI use vs. non-use (pooled relative risk [RR] 1.08, 95% confidence interval [CI] 0.82 to 1.43). Of note, the studies were conducted exclusively in European countries and there was a high degree of heterogeneity (I^2=99%). Also, due to the observational nature of the studies, a cause-effect relationship could not be concluded.

Selected details on the studies included in the meta-analysis[7] are available in Table 1 and are described below.

Table 1. Selected characteristics of observational studies evaluating risk of dementia with PPI use.[7,9-12]

Characteristics	Studies			
	de Souto Barreto et al, 2013	**Haenisch et al, 2015**	**Gomm et al, 2016**	**Booker et al, 2016**
Study design	Cross-sectional	Prospective cohort	Prospective cohort	Case-control
Study duration[a]	N/A	72 months (6 years); 4 follow-up assessments every 18 months	102 months (8.5 years); 6 follow-up assessments every 18 months[b]	N/A
Data source	IQUARE (study)	AgeCoDe (study)	AOK (German insurer)	Disease Analyzer database (IMS Health)
# of participants (PPI users vs. non-users)	6,275 (2,370 vs. 3,905)	3,076 (713 vs. 2,363)	73,679 (2,950 vs. 70,729)	11,956 cases 11,956 controls[c]
Mean age (years)	86	80	83	80
PPIs used	NS	NS	Most common: omeprazole, pantoprazole, esomeprazole	NS
Criteria for dementia	NS; determined by participating nursing home staff	DSM-IV; diagnosis determined by interviewer and geriatrician/geriatric psychiatrist	ICD-10 codes, reported at least twice in an interval	ICD-10 codes
Risk of dementia with PPI use vs. non-use (95% CI)	OR=0.666 (0.588 to 0.755)[d]	HR=1.38 (1.04 to 1.83)	HR=1.44 (1.36 to 1.52)	OR=0.94 (0.90 to 0.97)

[a]Study duration not necessarily tantamount to duration of PPI use. Duration of PPI use not specified in most studies.
[b]Last follow-up interval was 12 months.
[c]Cases were defined as primary care patients with dementia; controls were matched patients without dementia.
[d]The authors interpreted these results as patients with dementia were less likely to take PPIs.

AgeCoDe=German Study on Aging, Cognition and Dementia in Primary Care Patients; AOK=Allgemeine Ortskrankenkassen; CI=confidence interval; DSM-IV=Diagnostic and Statistical Manual, fourth edition; HR=hazards ratio; ICD-10=International Classification of Diseases, tenth revision; IMS Health=QuintilesIMS; IQUARE=a multicenter, individually-tailored controlled trial conducted in nursing homes in France; N/A=not applicable; NS=not specified; OR=odds ratio; PPI=proton pump inhibitor

de Souto Barreto et al. investigated the factors associated with PPI use among nursing home (NH) residents.[9] The definition of current PPI use was obtained from prescription history provided by NH staff. They obtained data from the IQUARE study, a multicentric individually-tailored control trial completed in south-western France. Other medications and conditions potentially associated with PPI use were also examined. PPI use was prevalent (37.8%); peptic ulcer disease and non-steroidal anti-inflammatory drug (NSAID) use were important indicators for PPI therapy but were linked to a small fraction of PPI prescriptions. The authors hypothesized that the NH residents' high prescriptions rates were possibly due to the particular vulnerability to GI complications. The odds ratio (OR) illustrated a decreased use of PPIs among patients with dementia. Overall, the investigators concluded that there is a need for prospective studies evaluating predictors of PPI use as well as potential risks associated with PPI use.

Haenisch et al evaluated data from a longitudinal, multicenter cohort German study (Aging Cognition and Dementia in Primary Care Patients [AgeCoDe]), to research a potential association between use of PPIs and dementia in elderly patients aged greater than 75 years.[10] After adjustment for potential confounders (age, sex, education, ApoE4 allele status, polypharmacy) and comorbidities (depression, diabetes, ischemic heart disease, and stroke), the investigators determined that the patients receiving a PPI had a significantly increased risk of any dementia compared to non-users.

Gomm et al also conducted a prospective cohort study to determine the risk of incident dementia with any PPI use.[11] They analyzed data from Germany's largest health insurer, Allgemeine Ortskrankenkassen (AOK). Participants were aged ≥75 years and free of dementia at baseline. Regular PPI use was defined as receiving at least 1 PPI prescription in each quarter of an interval. Potential confounders (age, sex, polypharmacy, and comorbidities of stroke, depression, ischemic heart disease, and diabetes) were included in the analysis. The study found that use of PPIs was associated with a significant increase in the risk of incident dementia, after accounting for potential confounders (hazard ratio [HR] 1.44, 95% CI 1.36-1.52). As referenced in Table 2, the risk of incident dementia with PPI use was determined to be inversely related to age (age-adjusted HR: [75-79 years] 1.69, 95% CI 1.49-1.92, [80-84 years] 1.49, 95% CI 1.35-1.66, [≥85 years] 1.32, 95% CI 1.22-1.43).

Table 2. PPI-associated risk of incident dementia. Adapted from a prospective cohort by Gomm et al.[11]

	Risk of Incident Dementia					
	75-79 y		80-84 y		≥85 y	
Risk Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
PPI use calulated[a]						
With potential confounding factors	1.69 (1.49-1.92)	<.001	1.49 (1.35-1.66)	<.001	1.32 (1.22-1.43)	<.001
Without potential confounding factors	2.01 (1.78-2.28)	<.001	1.68 (1.51-1.86)	<.001	1.35 (1.25-1.46)	<.001
Age[b]	1.128 (1.109-1.148)	<.001	1.092 (1.076-1.107)	<.001	1.045 (1.040-1.051)	<.001
Sex[c]	1.10 (1.04-1.16)	<.001	1.15 (1.09-1.21)	<.001	1.16 (1.11-1.22)	<.001
Depression	1.44 (1.34-1.54)	<.001	1.35 (1.27-1.43)	<.001	1.15 (1.09-1.21)	<.001
Diabetes	1.16 (1.10-1.22)	<.001	1.04 (0.99-1.08)	.15	0.99 (0.95-1.03)	.45
Stroke	1.78 (1.59-2.00)	<.001	1.37 (1.23-1.54)	<.001	1.15 (1.04-1.27)	.01
Ischemic heart disease	0.94 (0.89-0.99)	.02	0.96 (0.92-1.00)	.07	0.90 (0.87-0.93)	<.001
Polypharmacy[d]	1.27 (1.21-1.34)	<.001	1.21 (1.15-1.26)	<.001	1.05 (1.02-1.09)	.003

Most recently, a case-control study was published in which Booker and colleagues included patients aged 70-90 years seen in primary care centers in Germany with first diagnosis of dementia documented during the index period of January 2010 to December 2014.[12] These patients were matched to controls (patients without dementia, 1:1) on the basis of age, sex, type of health insurance, and physician. Practice visit records were used to verify 10 years of continuous follow-up prior to the index date. The purpose of this study was to estimate risk factors of dementia in German primary care patients. The study showed an increased risk of dementia with many variables such as diabetes, coronary heart disease, and

Parkinson's disease. However, they found that PPI use was associated with a decreased risk of dementia. A decrease in risk of dementia was also appreciated in patients using statins (OR 0.94, 95% CI 0.90 to 0.99) and antihypertensive drugs (OR 0.96, 95% CI 0.94 to 0.99). Booker et al concluded that further research is necessary to characterize the relationship between PPI use and risk of dementia.

Summary

In summary, recently published studies have revealed a possible association between PPI use and dementia in the elderly.[8,10,11] The evidence remains disputable with data demonstrating both increases and decreases in risk of dementia with PPI use. At this time, the FDA has not recommended any changes to the drug labeling for PPIs with regard to increased risk for dementia. Large randomized, prospective trials are needed to firmly establish a direct cause and effect relationship between PPIs and their potential adverse effects.

References

1. Proton pump inhibitors – drug class overview. In: Clinical Pharmacology. [updated: unknown; accessed 1/17/17]. https://hubnet.buffalo.edu:2067/pharmacology/resources/overviews?id=1217047.
2. Prilosec® (omeprazole) [package insert]. Wilmington, DE: AstraZeneca Pharmaceutical LP; 2016.
3. Nexium® (esomeprazole) [package insert]. Wilmington, DE; Astrazeneca Pharmaceuticals LP; 2016.
4. Proton pump inhibitors. In: Facts and Comparisons. [updated 01/18/17; accessed 2/22/17]. http://hubnet.buffalo.edu:2053/lco/action/search?q=proton%20pump%20inhibitors&t=name#.
5. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA*. 2015;314(17):1818-1831.
6. Rotman SR, Bishop TF. Proton pump inhibitor use in the U.S. ambulatory setting, 2002-2009. *PLoS One*. 2013;8(2):e56060.
7. Wijarnpreecha K, Thongprayoon C, Panjawatanan P, Ungprasert P. Proton pump inhibitors and risk of dementia. *Ann Transl Med*. 2016;4(12):240.
8. Neurocognitive Disorders. In: *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition. Arlington, VA: American Psychiatric Association; 2013. http://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596. Accessed February 23, 2017.
9. de Souto Barreto P, Lapeyre-Mestre M, Mathieu C, et al. Prevalence and associations of the use of proton-pump inhibitors in nursing homes: a cross sectional study. *J Am Med Dir Assoc*. 2013;14(4):265-269.
10. Haenisch B, von Holt K, Wiese B, et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. *Eur Arch Psychiatry Clin Neurosci*. 2015;265(5):419-428.
11. Gomm W, von Holt K, Thome F. et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurol*. 2016;73(4);410-416.
12. Booker A, Jacob LE, Rapp M, Bohlken J, Kostey K. Risk factors for dementia diagnosis in German primary care practices. *Int Psychogeriatr*. 2016;28(7):1059-1065.

Cardiovascular Risk of the Selective NSAID Celecoxib: Review of the PRECISION Trial

Nick Ladziak, PharmD

Celecoxib (Celebrex®) is a non-steroidal anti-inflammatory drug (NSAID) approved for several uses, including the management of signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA), and the management of acute pain in adults.[1] Celecoxib selectively targets the cyclo-oxygenase (COX)-2 isoform, which is responsible for mediating pain and inflammation, as opposed to the COX-1 isoform, which has been linked to toxic gastrointestinal (GI) effects.[2] This selectivity suggests that celecoxib can decrease pain without producing adverse GI effects, unlike other, non-selective NSAIDs. At present, celecoxib is the only COX-2 selective NSAID available in the United States. Rofecoxib, a previously available COX-2 selective NSAID, was withdrawn from the market based on findings from a placebo-controlled trial indicating an increase in adverse cardiovascular (CV) events with the drug. These data, combined with reports of CV events with high doses of celecoxib (400 mg twice daily) in another trial, spurred the Food and Drug

Administration (FDA) to require a CV safety trial for celecoxib.[3] The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial was designed to evaluate the safety and efficacy of celecoxib compared to nonselective NSAIDs, ibuprofen and naproxen, with respect to a composite CV outcome.

The PRECISION trial was a multinational, randomized, double-blind, triple-dummy noninferiority study involving patients with symptomatic OA or RA and with established or at high risk for CV disease.[2,4] The investigators defined established or high CV risk as 1 of the following: coronary disease, occlusive disease of non-coronary arteries, type I or type II diabetes mellitus, or high risk of atherosclerotic vascular disease.[5] Patients were stratified by type of arthritis, aspirin use, and geographic region and then randomized in a 1:1:1 ratio to receive celecoxib 100 mg twice daily, ibuprofen 600 mg 3 times daily, or naproxen 375 mg twice daily.[2,4,5] Arthritic pain was assessed using a visual analogue scale (VAS, possible score range 0 to 100 mm). Patients with RA could receive higher doses of these medications, up to 200 mg twice daily for celecoxib, 800 mg 3 times daily for ibuprofen, and 500 mg twice daily for naproxen. Patients with OA could not receive higher doses of celecoxib, but higher doses of ibuprofen or naproxen were allowed. All patients were given esomeprazole 20-40 mg for GI protection during the trial.[2,4] Patients taking aspirin at doses of 325 mg or less, daily, were allowed to continue aspirin therapy during the trial.

The primary composite outcome was the first occurrence of an adverse CV event, as defined by Antiplatelet Trialists Collaboration (ATC) criteria.[2] Events meeting the ATC criteria were death from CV causes, including hemorrhagic death, nonfatal myocardial infarction (MI), or nonfatal stroke. Secondary outcomes included clinically significant GI events and a composite endpoint which included the events in the primary composite endpoint plus coronary revascularization or hospitalization for unstable angina or transient ischemic attack. Clinically significant GI effects are listed in the supplementary appendix and include gastroduodenal, small bowel or large bowel hemorrhage, gastric outlet obstruction, gastroduodenal, small bowel or large bowel perforation, acute GI hemorrhage of unknown origin, or symptomatic gastric or duodenal ulcer.[5] Significant renal events, iron deficiency anemia of GI origin, and hospitalization for heart failure or hypertension were also investigated as tertiary outcomes.[2] All events were adjudicated by an external committee without knowledge of study treatment assignments.

The primary noninferiority comparator for celecoxib was naproxen, but noninferiority comparisons were also planned between celecoxib and ibuprofen and between naproxen and ibuprofen.[2] Intention-to-treat and per-protocol (on-treatment) analyses were employed. The investigators determined that 762 events were needed to achieve 90% power to determine noninferiority. However, the observed event rate was lower than expected and the data and safety monitoring committee and the FDA recommended amending the study protocol. The investigators adjusted the study power to 80% and modified the upper limit for the 97.5% confidence interval (CI, to indicate noninferiority) to 1.40; using these parameters, they determined 580 events were needed in the intention-to-treat population and 420 events in the on-treatment population. The investigators used a Cox proportional-hazards model to calculate hazard ratios (HR) and CIs, which was appropriate for comparing the occurrence of events among the groups. A 1-sided p-value <0.025 was considered statistically significant for the primary endpoint. For the secondary analyses, 2-sided p-values <0.05 indicated statistical significance. No adjustments were made for multiple comparisons.

A total of 24,081 patients were included in the trial, and they were equally distributed among the 3 treatment groups.[2] Patient characteristics at baseline were similar across groups. Of the included patients, 2,436 (10.1%) had a primary diagnosis of RA while the remaining patients had a primary diagnosis of OA. Pain scores were similar at approximately 54 mm on the VAS. The majority of patients (77.2%) had no history of CV disease. Previous aspirin use was similar across groups (~46% in each arm). Statistically significant differences were reported in systolic blood pressure ($p=0.044$), but the mean blood pressure was similar across groups (~125 mmHg in each group). The average study treatment duration was 20.3 ± 16 months, and the average follow up duration was 34.1 ± 13.4 months. During the trial, approximately 68.8% of patients discontinued the study drug, and approximately 27.4% of patients discontinued follow-up.

With regard to the primary outcome, using both intention-to-treat and on-treatment analyses, celecoxib was determined to be noninferior to naproxen and ibuprofen.[2] In the intention-to-treat analysis, primary outcome events were reported in 188 patients taking celecoxib (2.3%), compared to 201 patients taking naproxen (2.5%; HR 0.93, 95% CI 0.76 to 1.13) and 218 patients taking ibuprofen (2.7%; HR 0.85, 95% CI 0.70 to 1.04; $p<0.001$ for noninferiority in both comparisons). In

the on-treatment analysis, primary outcome events were reported in 134 patients taking celecoxib (1.7%), compared to 144 patients taking naproxen (1.8%; HR 0.90, 95% CI 0.71 to 1.15) and 155 patients taking ibuprofen (1.9%; HR 0.81, 95% CI 0.65 to 1.02; p<0.001 for noninferiority in both comparisons). The differences in rates of any CV event, the secondary composite outcome, were not significant when comparing celecoxib to naproxen or ibuprofen. Of note, the rate of nonfatal MI was significantly higher with ibuprofen compared to naproxen (HR 1.39, 95% CI 1.01 to 1.91).

For other outcomes, celecoxib showed a similar rate of clinically significant GI events compared to naproxen (HR 0.97, 95% CI 0.67 to 1.40) and to ibuprofen (HR 0.76, 95% CI 0.53 to 1.08).[2] The rate of iron-deficiency anemia was significantly lower for celecoxib compared to naproxen (HR 0.47, 95% CI 0.31 to 0.71) and to ibuprofen (HR 0.51, 95% CI 0.33 to 0.77). Combining the results for these 2 adverse outcomes, the investigators determined that the composite of serious GI events was lower with celecoxib compared to naproxen (HR 0.71, 95% CI 0.54 to 0.93) and to ibuprofen (HR 0.65, 95% CI 0.50 to 0.85). Serious renal events were significantly lower in the celecoxib group compared to the ibuprofen group (HR 0.61, 95% CI 0.44 to 0.85), but not compared to the naproxen group (HR 0.79, 95% CI 0.56 to 1.12). Similarly, celecoxib showed a significantly lower rate of hospitalization for hypertension compared to ibuprofen (HR 0.60, 95% CI, 0.36 to 0.99) but not to naproxen (HR 0.69, 95% CI 0.41 to 1.17). With regard to analgesia, naproxen showed significantly greater reductions in VAS scores compared to celecoxib and to ibuprofen (mean changes from baseline, respectively: -9.3 mm, -9.5 mm, and -10.2 mm), though the authors highlight that the differences in scores may not be clinically significant.

Based on the results of the trial, the authors concluded that celecoxib, administered at moderate doses, was noninferior to naproxen or ibuprofen with regard to CV safety.[2] Further safety analyses showed that celecoxib was no worse for a broader category of CV events, and potentially safer with regard to GI and renal outcomes.

The authors acknowledge some limitations of the trial. One limitation was the celecoxib dosing for patients with OA, restricted to a total daily dose of 200 mg.[2] In practice, higher doses of the drug may be used off-label to treat OA pain. These higher doses may carry a greater risk; this was not fully addressed in this study, given the dose restriction in the majority (~90%) of the study population. A dose-dependent increase in risk of CV events was observed in another study using celecoxib.[3] Another issue was adherence to study drugs.[2] The investigators reported that 69% of patients discontinued treatment for various reasons including patient choice, an adverse event, or insufficient clinical response, among others.[5] Discontinuation rates were similar between groups but most occurred within 1 year of randomization; thus, interpreting the study results in the context of the overall study duration may not be appropriate. The use of esomeprazole in all patients may have affected the observed GI event rates. The GI data should be interpreted carefully as the rate of clinically significant GI events was similar across groups, though the rate of iron deficiency anemia was lower in the celecoxib group. The investigators based their conclusion regarding GI safety of celecoxib on the composite of these 2 outcomes. Lastly, the PRECISION trial may have a limited scope as there are other NSAIDs used in daily practice which were not investigated in the study. Some of these, like diclofenac, are recognized as having a potentially higher CV risk compared to celecoxib, but this conclusion would require head-to-head evaluation.[6]

NSAIDs remain commonly used medications for arthritis pain.[7] The PRECISION trial provides evidence for safe use of moderate doses of celecoxib with regards to CV events, compared to naproxen and ibuprofen.[2] Additionally, the investigators showed a similar safety profile with celecoxib for serious GI adverse events and a significantly lower rate of renal adverse events compared to ibuprofen. Caution should be used when considering higher doses of celecoxib in patients with arthritis, as these doses may carry additional safety concerns and were not thoroughly examined in this study.

References

1. Celebrex® [package insert]. New York, NY: Pfizer Inc.; 2016.
2. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. *N Engl J Med.* 2016;375(26):2519-2529.
3. Solomon SD, McMurray JJV, Pfeffer MA, et al. Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention. *N Engl J Med.* 2005;352(11):1071-1080.

4. Becker MC, Wang TH, Wisniewski L, et al. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal antiinflammatory agents in patients with arthritis. *Am Heart J.* 2009;157(4):606-612.
5. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis [supplemental appendix]. Available at: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1611593/suppl_file/nejmoa1611593_appendix.pdf. Accessed January 30, 2017..
6. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med.* 2011;8(9):e1001098.
7. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res.* 2012;64(4):465-474.

Author Biographies

Patrick McCabe, PharmD, MBA
Dr. McCabe received his Doctor of Pharmacy degree from the St. John Fisher Wegmans School of Pharmacy and Master of Business Administration degree from the St. John Fisher School of Business. Prior to that, he received a Bachelor of Science in Biology from the St. John Fisher College. Dr. McCabe is currently a PGY-1 pharmacy practice resident at the UB/Middleport Family Health Center. He is very interested in expanding the role of ambulatory care pharmacy in the community setting and in entrepreneurship.

Emily Leppien, PharmD
Dr. Leppien received her Doctor of Pharmacy degree from the Albany College of Pharmacy and Health Sciences. She is currently the PGY-1 pharmacy practice resident at the Buffalo Psychiatric Center. Her professional interests include clinical psychopharmacology, inpatient psychiatry, substance abuse, and pharmacy education. Upon completion of her program, Dr. Leppien plans to pursue a position as a PGY-2 psychiatric pharmacy practice resident and obtain board certification as a pharmacotherapy specialist.

Anthony Chiappelli, PharmD
Dr. Chiappelli received his Doctor of Pharmacy degree from the University of Pittsburgh School of Pharmacy. He is currently the PGY-1 pharmacy practice resident at Lifetime Health Medical Group. Dr. Chiappelli has several years of experience in community pharmacy practice with a strong interest in ambulatory care. He hopes to pursue a career in ambulatory care near his hometown of St. Mary's, Pennsylvania.

Nick Ladziak, PharmD
Dr. Ladziak received his Doctor of Pharmacy degree from the UB SPPS. He is the current PGY-2 ambulatory care pharmacy practice resident at Buffalo Medical Group. His professional interests include ambulatory care, both preventive medicine and chronic disease state management, as well as academia and pharmacy informatics. After completion of his residency, Dr. Ladziak plans to pursue a career as a clinical pharmacist in an ambulatory care setting, continue to serve as a preceptor for pharmacy students, and achieve board certification as an ambulatory care pharmacy specialist.

Editors

Terry Dunn, PharmD
Dr. Dunn received both her BS in Pharmacy and PharmD from the UB SPPS. She also completed a hospital pharmacy residency at New England Medical Center in Boston. She has had extensive experience as a pharmacist in various settings, including practicing in a traditional role in hospitals as a Clinical Pharmacy Specialist. She has also served as a Science Specialist at a law firm, working with a team of lawyers defending pharmaceutical companies in product liability lawsuits. In addition, she has participated on an FDA contract updating and rewriting drug labels. She is currently a

Clinical Assistant Professor at the UB SPPS and Coordinator for the Center for Health Outcomes, Pharmacoinformatics, and Epidemiology (HOPE).

Irene Reilly, PharmD, BCPS
Dr. Reilly received her PharmD from the University of Illinois at Chicago (UIC) College of Pharmacy after receiving her BA in Economics from the University of Chicago. She completed PGY-1 and PGY-2 residencies at the UIC College of Pharmacy, specializing in drug information. She is currently a Clinical Assistant Professor at the UB SPPS and she leads the New York State Medicaid Drug Information Response Center.

Please address any comments or corrections to Dr. Reilly at irenehon@buffalo.edu.