Volume 25 • Issue 4 www.pswi.org

July/August 2022

The Journal

of the Pharmacy Society of Wisconsin

Frist Annual

CHRIS DECKER SCHOLARSHIP GOLF OUTING

Recap

July/August 2022

Continuing Education

Features

Original Work

Review Articles

Writing Club

PSW News

Spotlight

The Journal
of the Pharmacy Society of Wisconsin

Pharmacist Editor
AMANDA MARGOLIS, PharmD, MS, BCACP

Managing Editor & Creative Content Director
MEGAN GRANT, mgrant@pswi.org

Copy Editor
JENNIFER PITTERLE

CE Coordinator
PATRICIA THORNEWELL, PharmD

Peer Review Coordinators
MARISA GONINEN, PharmD, BCACP
MICHAEL NAGY, PharmD
KHYATI PATEL, PharmD
SARAH PEPPARD, PharmD, BCPS, BCCCP

ID Corner Series Coordinator
LYNNE FEHRENBACHER, PharmD, BCPS-AQ ID

Precepting Series Coordinator
MELISSA THEESFELD, PharmD

Open Access Coordinator
AMANDA EGBERT, 2024 PharmD Candidate

The Journal of the Pharmacy Society of Wisconsin is a professional publication for original research, review, experience, and opinion articles that link science with contemporary pharmacy practice to improve patient care. Together we can inspire each other to advance our profession with the single purpose of enhancing the lives of our patients.

Send correspondence to:
Megan Grant, Pharmacy Society of Wisconsin
701 Heartland Trail, Madison, WI 53717, phone: 608-827-9200,
fax: 608-827-9292, thejournal@pswi.org

Authors are encouraged to submit manuscripts to be considered for publication in *The Journal*. For Author Guidelines, see www.jpswi.org

Advertising inquiries:
Megan Grant, Pharmacy Society of Wisconsin, 701 Heartland Trail, Madison, WI 53717, phone: 608-827-9200, fax: 608-827-9292, mgrant@pswi.org

The Journal of the Pharmacy Society of Wisconsin is the official publication of the Pharmacy Society of Wisconsin. Subscription included in membership dues. Published bimonthly by the Pharmacy Society of Wisconsin, 701 Heartland Trail, Madison, WI 53717. Opinions expressed by contributors do not necessarily reflect those of PSW.

UpFront: Stepping Up to the Plate

by Amanda Margolis, PharmD, MS, BCACP

The Pharmacy Society of Wisconsin (PSW) engages in a number of opportunities for those in the pharmacy profession. These opportunities include, but are not limited to:

- Education offered through home study and at conferences
- Networking opportunities to engage and share ideas across the state of Wisconsin
- Legislative engagement to promote advancement of pharmacy practice
- Resources such as toolkits and manuals

Periodically, it is reasonable to reflect on your professional engagement. I would encourage you to reflect on your current engagement in PSW to see if there are opportunities where you could step up to the plate and become more involved or involved in a new way. My primary involvement in PSW has always been with *The Journal*. When I was a student, I contributed manuscripts under the mentorship of an advisor. Following residency, I became a peer reviewer, despite *The Journal's* lack of a formalized peer review program at the time. While PSW does a nice job of sharing ways to become engaged on their

Box 1: Topics of Interest

Burnout
Diversity, equity, and inclusion in pharmacy and health care
Endocrine and diabetes
Immunizations
Innovations in patient care
Medication safety
Mental health
Neurology
Nutrition and gastrointestinal health
Population health
Public health
Specialty pharmacy
Telehealth

FIGURE 1. Become a Peer Reviewer!

Peer Review Information

Peer review is an essential step for ensuring the quality of the manuscripts published in *The Journal*. We use a double-blind peer review process for manuscript review. Peer reviewers consider the appropriateness of the manuscript for *The Journal*, ensure the writing is clear and concise (i.e. figures are consistent with text, key messages are highlighted), and verify that the article is appropriately cited. Peer reviewers also ensure the conclusions from original work are appropriate for the rigor of the evaluation methods.

Details:

- Areas of expertise are identified, and articles are assigned based on knowledge and interest of specific article topics
- Peer reviews are assigned every 3 months, 6 months, or annually based on the reviewer's preference
- 1-3 independent peer reviewers are assigned to a manuscript
- Approximately 2-3 hours should be allocated to complete a thorough review and provide written feedback
- Reviewers serve to provide feedback focused on the content of the manuscript

Expectations:

- A final review should be returned within 2 weeks
- Manuscripts are confidential and should not be discussed until after the article is published
  - Senior reviewers working with new peer reviewers to foster peer reviewing skills is appropriate and encouraged
- Any potential conflicts of interest should be communicated to the editor, Amanda Margolis amargolis@pswi.org
- Reviewers cannot directly contact the writer with exception to their written review
- Recommendations and requests for more information should be submitted to the peer review coordinator
- Reviewers must check that reasonable statistical tests are used and should check totals and tables for accuracy
- A written review with feedback on the document, a completed Peer Review Evaluation Criteria Checklist (linked below), and a recommendation regarding publication must be submitted to the editor

Interested in becoming a peer reviewer? Fill out the survey below:
https://uwmadison.co1.qualtrics.com/jfe/form/SV_c1PcsvlAitCPTcC

Sign-ups are checked monthly; you will receive an email once you are added to the peer reviewer database.

Editor: Amanda Margolis amargolis@pswi.org

website, and we now have a formalized *JPSW* peer review program that anyone can sign up for (Figure 1), there may be opportunities you are interested in that are not formally posted. In my case, I initially became more involved in *JPSW*, and subsequently PSW, by emailing the editor to offer assistance. Over time, I was asked to join what is now the *JPSW* Editorial Advisory Committee and eventually became the Pharmacist Editor of *The Journal*.

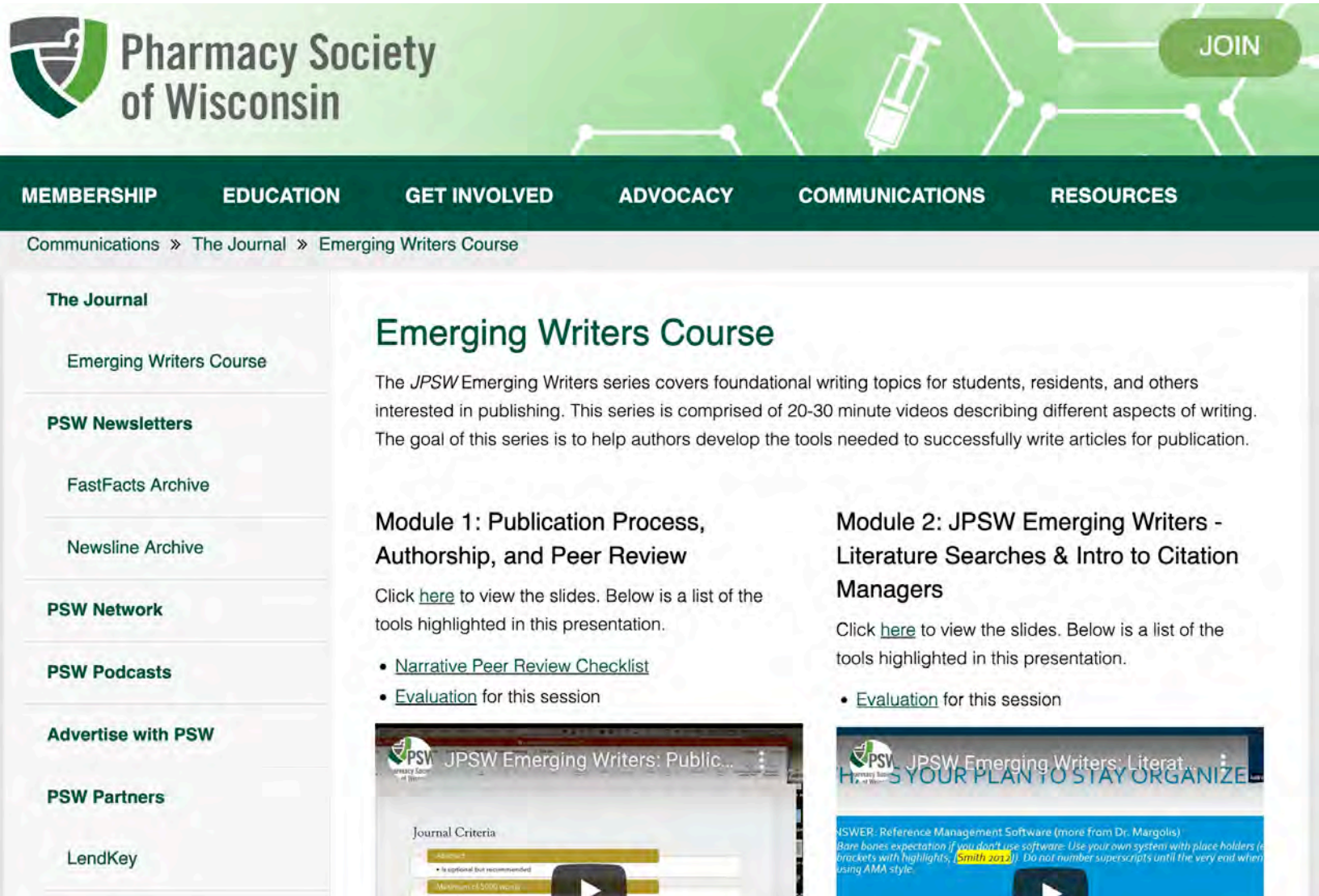
At *JPSW* we have several opportunities for involvement. The least time intensive and easiest to sign up for is to become a peer reviewer (Figure 1). If you are new to peer reviewing, we have resources posted that explain the peer review process and what to look for when conducting a review. No previous experience is necessary.

We also encourage all members of PSW to consider contributing a manuscript to *JPSW* for publication. Starting in 2023, we are no longer assigning specific issue themes. Instead, we have more flexible topics of interest (Box 1) that potential authors can review to help guide article topics. Articles are not required to be on those topics, but if you would like to write an article and are unsure of where to begin, reviewing the list in Box 1 may be a starting point. If you are a novice writer, feel free to use the *JPSW* Emerging Writers course (Figure 2). Topics include literature searches, writing structure, citations, and avoiding common grammatical errors. Preceptors and residency directors, feel free to share this program with trainees even if they are not planning to write for *JPSW.*

Lastly, there are larger leadership roles within JPSW. These include being a series coordinator, a peer review coordinator, or a member of the *JPSW* Editorial Advisory Committee. If one of these roles sounds interesting to you or you have any questions about submitting a manuscript, please don't hesitate to reach out! This may be your opportunity to step up to the plate!

- Amanda Margolis, PharmD, MS, BCACP
Pharmacist Editor

FIGURE 2. *JPSW* Emerging Writers Program



PHARMACIST CE:

The X-Factor: Overcoming DOAC Barriers in OAC Eligible Patients

by Christi Ann Albert, PharmD, BCPS, Kristina Yokes, PharmD, BCACP, Anne E. Rose, PharmD

Direct oral anticoagulants (DOACs) have emerged as a preferred anticoagulant in eligible patients who have atrial fibrillation (AF) or venous thromboembolism (VTE).[1-3] Prior to DOACs, anticoagulation options included vitamin K antagonists (VKAs) and parenteral agents. DOACs are now recommended over VKAs by societal guidelines given their efficacy and improved or similar bleeding risks compared to VKAs.[1-3] DOACs offer key advantages, such as rapid onset, few drug-drug interactions, and limited dietary interactions. However, potential barriers exist, including cost and provider/patient knowledge of a newer class of medications (Table 1).

Warfarin, a vitamin K antagonist,

CE FOR **PHARMACISTS**

COMPLETE ARTICLE AND CE EXAM AVAILABLE ONLINE: **WWW.PSWI.ORG**

Learning Objectives

- Identify patient populations eligible for DOACs and when DOAC use is controversial or contraindicated.
- Compare and contrast characteristics of VKAs with DOACs.
- Apply national organizational guidelines for AF and VTE when choosing an anticoagulant.
- Describe ways to overcome cost barriers for DOACs.

Abbreviations

ACC - American College of Cardiology
AF - atrial fibrillation
AHA - American Heart Association
DOAC - direct oral anticoagulant
DVT - deep vein thrombosis
HRS - Heart Rhythm Society
OAC - oral anticoagulant
PE - pulmonary embolism
VKA - vitamin K antagonist
VTE - venous thromboembolism

TABLE 1. Oral anticoagulant options: Comparing VKA to DOACs

Warfarin (Coumadin®)		*Direct Oral Anticoagulants (Eliquis®, Xarelto®, Pradaxa®, Savaysa®)*	
⚠	No longer first line option for AF or VTE	✓	Preferred first line option for AF and VTE given efficacy and lower overall rates of intracranial hemorrhage.
✓	> 60 years' experience with many indications	⚠	Fewer approved indications – still waiting for data in some conditions that could cause stroke or thromboembolism
✓	Ability to check INRs as a measure of efficacy/safety	✓	No need for frequent drug-levels
⚠	Narrow therapeutic range – Poor outcomes associated with out-of-range INRs or low time in therapeutic range (TTR ≤ 65%)[17]	✓	Wide therapeutic index
⚠	Many drug-drug interactions including herbal supplements and over-the-counter medications	✓	Fewer drug interactions
✓	Effect of any drug interaction can be monitored with INR testing and dose adjustments can be made to accommodate interaction	✗	Phenobarbital, phenytoin, carbamazepine, St John's Wort, and rifampin are contraindicated with DOACs
⚠	Need for consistent diet (vitamin K containing foods, alcohol, cranberry juice, grapefruit juice all affect INR)	✓	Almost no dietary interactions outside of grapefruit juice and alcohol
✓	Readily reversible with phytonadione (vitamin K) or prothrombin complex concentrates (PCC)	✓	Reversal agents for severe bleeding are available (including prothrombin complex concentrates (PCCs), andexanent alfa (Andexxa®) and idarucizumab (Praxbind®)
⚠	Variable dosing that can change with each INR	✓	Consistent dosing with infrequent dose adjustments
✓	Inexpensive	⚠	Can be cost prohibitive for some patients. Manufacturer and industry sponsored assistance programs are available to offset higher upfront cost

AF = atrial fibrillation; VTE = venous thromboembolism; DOAC = direct oral anticoagulant

was initially approved in 1954.[4] It acts by inhibiting the synthesis of Vitamin-K dependent clotting factors, which include Factors II, VII, IX, and X, along with proteins C and S.[4] In 2010, dabigatran (Pradaxa®) was the first DOAC approved by the Food and Drug Administration (FDA) in the United States.[5] Dabigatran is a direct thrombin inhibitor, which prevents the conversion of fibrinogen to fibrin.[5] Factor Xa inhibitors followed, which prevent clot formation by decreasing thrombin generation. These include rivaroxaban (Xarelto®) in 2011, apixaban (Eliquis®) in 2012, and edoxaban (Sayvasa®) in 2015.[6-8]

Notably, there are some patient populations where DOACs are contraindicated or where the risk/benefit should be discussed prior to use (Figure 1).[9] This article focuses on the two most common indications for DOACs, AF and venous thromboembolism (VTE), by providing clinical rationale along with strategies to overcome barriers to DOAC usage.

Atrial Fibrillation

Atrial fibrillation (AF) is one of the most common arrythmias prevalent worldwide and is responsible for 15% of strokes.[10,11] Patients with AF have a 5-fold increased risk of stroke when compared to patients without AF. AF-induced thromboembolic strokes are associated with increased morbidity, mortality, and costs when compared to strokes from other causes. Given the rates of obesity and diabetes, along with an aging population, projections estimate that the prevalence of AF will at least double in the next 25 years.

Figure 2 outlines the different types of AF.[12] Older guidelines classified AF as either valvular or nonvalvular AF.[1] Newer versions of published guidelines are transitioning to new terminology, which focuses on cause and length of time AF is present. The guidelines state oral anticoagulants (OAC) should be considered for atrial flutter or AF including paroxysmal, permanent, and chronic (also called long-standing).

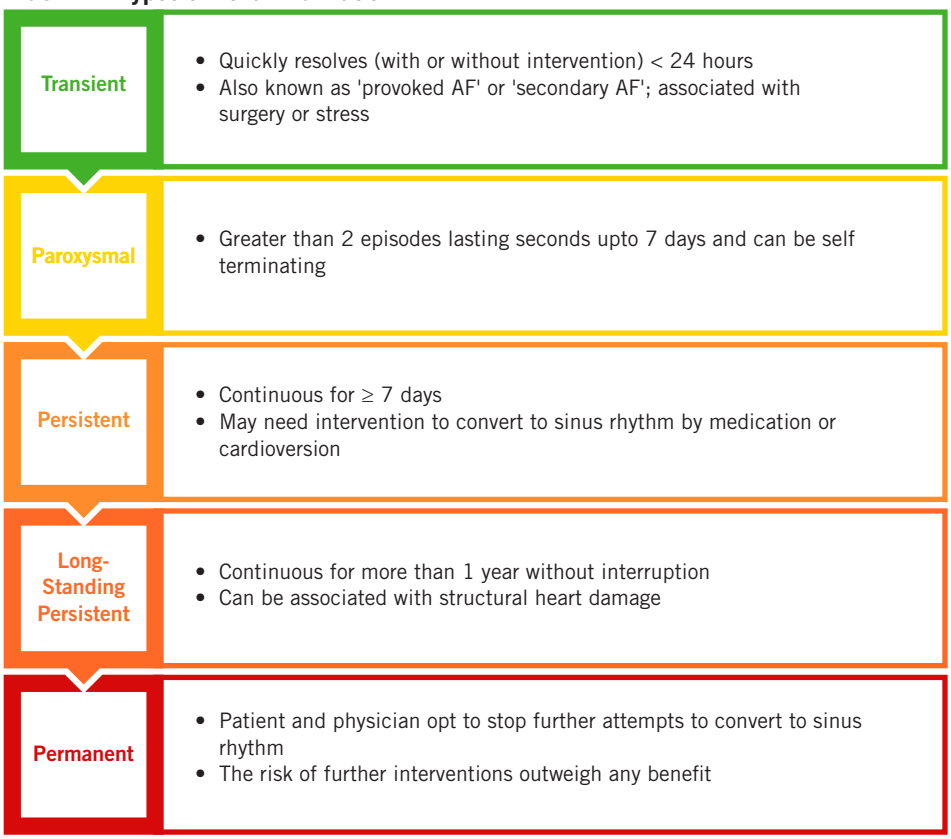
The risk of stroke from AF can be calculated using a risk assessment tool. Previous recommendations by the American Heart Association, American College of Cardiology and Heart Rhythm Society (AHA/ACC/HRS) Atrial Fibrillation Guidelines ("the AF Guidelines") had been

FIGURE 1. Contraindicated or Controversial DOAC Use[1-9]

DOAC Use is Contraindicated
Indications in which DOACs have proven harmful or inefficacious • Mechanical heart valve replacement • Left Ventricular Assist Device (LVAD) • Triple Positive Antiphospholipid Antibody Syndrome (APS) • Embolic Stroke of Undetermined Source (ESUS) • Moderate to Severe Mitral Valve Stenosis
Within 3 months of bioprosthetic heart valve replacement
Severe hepatic impairment
Pregnancy or breastfeeding
Female (sex assigned at birth) of childbearing potential not using reliable contraception
Taking medications known to majorly interact with DOACs*
Unable to access DOAC due to cost without access to financial assistance
DOAC Use is Controversial (Discuss Risk/Benefits Prior to Use)
Off-label indications
VTE associated with gastrointestinal (GI) or genitourinary (GU) cancers
Moderate hepatic impairment
Severe renal impairment (CrCl<30mL/min)**
Taking multiple inhibitors of DOAC metabolism in setting of moderate impaired renal function
Poor medication adherence
Treatment failure on therapeutic warfarin or low molecular weight heparin
History of gastric bypass or removed portions of GI tract

**Phenytoin, carbamazepine, phenobarbital, St John's Wort, Rifampin are examples*
***indication and DOAC dependent*
DOAC = direct oral anticoagulant; CrCl - creatinine clearance; GI = gastrointestinal; VTE = venous thromboembolism
Reproduced with permission from the 2021 DOAC Playbook - Anticoagulation Forum©
Adapted to incorporate 2019 AHA/ACC/HRS AF Guidelines

FIGURE 2. Types of Atrial Fibrillation



Adapted from Healthline – Types of Atrial Fibrillation[12]. AF = atrial fibrillation

to use the $CHADS_2$ score.[1,13] The updated 2014 and revised 2019 AF Guidelines now recommend using the CHA_2DS_2VASc score to better identify at-risk patients. Criteria are outlined in Table 2. The changes from the $CHADS_2$ to the CHA_2DS_2VASc scoring tool includes 1 point for history of vascular diseases, including coronary artery disease (CAD), myocardial infarction (MI), coronary artery bypass grafting (CABG), cardiac stents or percutaneous coronary interventions (PCI), peripheral vascular disease (PVD), or venous stasis. The tool also includes 1 point for younger ages 65-74 years, and 1 point for female (sex assigned at birth). Female sex is a singular risk factor in the CHA_2DS_2VASc score and should not be considered without other risk factors for stroke. The female sex risk factor is age dependent and further impacts stroke risk starting at age 65. The change to utilizing the CHA_2DS_2VASc score has increased the proportion of people eligible for oral anticoagulation by 20%.[13,14] The updated 2019 AF guidelines strongly recommend oral anticoagulation (Level 1A recommendation; strongest strength and highest quality evidence) for any CHA_2DS_2VASc score ≥ 2 for men and ≥ 3 for women.[1] A notable change is that aspirin is no longer recommended for CHA_2DS_2VASc scores of 1 for men and 2 for women; therefore, OACs may be considered (Level 2b/C recommendation; weak benefit based on limited data) since there is a net positive clinical benefit of anticoagulation. Thus, females with AF and CHA_2DS_2VASc scores ≥ 2 remain OAC eligible, and for brevity, we will refer to any sex patient with AF and CHA_2DS_2VASc score ≥ 2 as OAC eligible.

Despite current guidelines recommending anticoagulation for patients with AF and CHA_2DS_2VASc scores ≥ 2, as many as 30%-40% of patients are not prescribed anticoagulation.[10,15] In half of these cases, it is provider preference not to anticoagulate.[10] The underuse of anticoagulation has been well studied and is multifactorial. Provider-perceived factors include patient fall risk, past recurrent falls, advanced age, perceived bleeding risks, cost and/or socioeconomic status, patient/provider spoken language mismatch, transportation barriers and/or rural residency, and prior or anticipated poor adherence and/or follow-up.[15,16] Other factors include under-diagnosis or lack of documentation of AF; lack of clarity if AF diagnosis is transient or temporary; lack of a documented CHA_2DS_2VASc score; provider practice area; provider familiarity with AF guideline recommendations; under-estimation of risk of stroke or overestimation of risk of bleeding.[10] Additionally, approximately 25% of patients within the first year of warfarin therapy for AF in the ATRIA study discontinued therapy, and this was a similar outcome in the ORBIT-AF registry.[18,19] Reasons for anticoagulation discontinuation

TABLE 2. Managing AF based on CHA_2DS_2VASc Scores and Thromboembolic/Stroke Risk[1,13]

Calculate CHA_2DS_2VASc Score: Add points in parenthesis for each applicable risk factor:
- Age (65-74=1; ≥75=2)
- Sex (Female=1)^
- CHF (1)
- HTN (1)
- DM (1)
- Vascular History (History of MI/CAD/CABG/Stenting/PCI, vascular disease, vascular plaques 1)
- History of stroke/TIA/ thromboembolism (2)

ACC/AHA/HRS OAC Guidance	*CHA_2DS_2VASc Score*	*Risk of stroke, TIA, systemic embolism*	
No OAC	0	Low	0.3%
OAC Eligible (Male^)	1		0.9%
OAC Eligible (Female^)	2	High	2.9%
OAC Recommended	3		4.6%
	4		6.7%
	5		10.0%
	6		13.6%
	7		15.7%
	8		15.2%
	9		17.4%

ACC/AHA/HRS 2019 AF Guideline Update no longer recommends aspirin as an alternative to OAC therapy no matter the CHA_2DS_2VASc risk score
- Omit OAC therapy for CHA_2DS_2VASc score = 0 male and ≤ 1 female^
- OAC Eligible for CHA_2DS_2VASc score = 1 for male and = 2 for female^
- OACs Recommended for CHA_2DS_2VASc score ≥ 2 for male and ≥ 3 for female^

^ Male / female sex refers to sex assigned at birth

Abbreviations: CHF=congestive heart failure, HTN=hypertension, DM=diabetes mellitus, MI=myocardial infarction, CAD=coronary artery disease, CABG=coronary artery bypass graft, PCI=percutaneous coronary intervention, TIA=transient ischemic attack, OAC=oral anticoagulant.

Adapted from 2019 ACC/AHA/HRS AF Guideline & Table 2 from Friberg L, Rosenqvist M, Lip GY. Eur Heart J. 2012;33(12):1500-1510

TABLE 3. Comparison of Prospective AF DOAC Trials[21-24]

Comparison Prospective AF DOAC trial efficacy outcomes				
	ARISTOTLE (apixaban)	*ROCKET-AF (rivaroxaban)*	*RE-LY (dabigatran)*	*ENGAGE AF-TIMI 48 (edoxaban)*
Composite – systemic embolism or stroke	**Superior**	Non-inferior	**Superior**	Non-inferior
Comparison Prospective AF DOAC trial safety outcomes				
Major bleeding	**Superior**	Non-inferior	Non-inferior	**Superior**
Intracranial hemorrhage (ICH)	**Superior**	**Superior**	**Superior**	**Superior**

included provider preference (47%), patient preference (21.1%), bleeding events (20.2%), frailty (10.8%), perceived high bleeding risk (9.8%), and poor adherence (4.7%).

Due to the low national adherence to guideline-based recommendations, AHA/HRS have started a quality improvement program called Get with the Guidelines (GWTG).[20] There are GWTG programs for multiple cardiovascular disease states, including GWTG-Coronary Artery Disease, GWTG-Heart Failure, and now GWTG-AFIB. The GWTG-AFIB quality improvement program started in 2013. Hospitals and health systems registered with the program and were provided with materials for providers and patients to facilitate guideline adherence. The GWTG-AFIB study participants were able to increase OAC prescribing in AF from a baseline of 60% (near the national average) to 90% after 18 months, and 95% after 4 years following enrollment into the program. Of the remaining 5% of patients not anticoagulated, the majority represented those with absolute contraindications to anticoagulation: prior major life-threatening bleeding, prior intracranial hemorrhage (ICH), recent high bleed risk operation, or severe critical comorbid illness (patients on comfort cares were excluded). The implementation of quality-based GWTG-AFIB was able to reduce the proportion of patients and providers who previously either had a preference against anticoagulation or who previously discontinued to as low as 2.7% and 2.6% respectively. The total of all prior stated contraindications to anticoagulation were in sum reduced from 20.9% to 12.9% over the four-year study period.

The 2019 AF Guidelines now recommend anticoagulation with DOACs over warfarin in eligible patients.[1] The preference for DOACs over warfarin is listed as a level 1A (strongest strength and highest quality evidence) recommendation. The guideline draws these conclusions from the primary AF DOAC drug trials, which cumulatively have included over 70,000 patients: ARISTOTLE (apixaban versus warfarin in AF), RE-LY (dabigatran versus warfarin in AF), ROCKET-AF (rivaroxaban versus warfarin in AF) and ENGAGE AF-TIMI48 (edoxaban versus warfarin in AF) and have demonstrated on average 50% reduced rate of intracranial hemorrhage, statistically significant reduced rates of bleeding, and improved mortality.[21-24] The clinical outcomes of these individual drug studies when compared to warfarin are listed in Table 3.

The risk of stroke is up to 20 times higher in the setting of combined AF and severe mitral stenosis.[1,10] However, AF caused by moderate to severe mitral valve stenosis and mechanical heart valves are considered contraindications to

TABLE 4. ARISTOPHANES Observational Data Summary[30]

	*Outcome**	*apixaban vs. warfarin*	*rivaroxaban vs. warfarin*	*dabigatran vs. warfarin*	*apixaban vs. rivaroxaban*	*apixaban vs. dabigatran*	*dabigatran vs. rivaroxaban*
Efficacy	Stroke / systemic embolism (SSE)	697 (1.33) vs. 1,299 (1.92)	1,203 (1.51) vs. 1,593 (2.21)	333 (1.42) vs. 428 (1.74)	710 (1.28) vs. 1,008 (1.47)	215 (1.12) vs. 333 (1.43)	334 (1.42) vs. 309 (1.29)
	Hazard Ratio (SSE)	0.64 [0.58-0.70]	0.79 [0.73-0.85]	0.82 [0.71-0.95]	0.80 [0.73-0.89]	0.72 [0.60-0.85]	1.10 [0.95-1.23]
Safety	Major Bleed (MB)	1,902 (1.77) vs. 3,770 (5.63)	4,607 (5.83) vs. 4,541 (5.45)	832 (3.60) vs. 1,229 (5.05)	1,948 (3.52) vs. 3,981 (5.88)	571 (2.98) vs. 832 (3.58)	836 (3.57) vs. 1,190 (5.02)
	MB Hazard Ratio	0.60 [0.56-0.63]	1.06 [1.02-1.10]	0.71 [0.65-0.78]	0.55 [0.53-0.59]	0.78 [0.70-0.87]	0.71 [0.65-0.78]
	Intracranial hemorrhage (ICH)	84 (0.36) vs. 210 (0.85)	452 (0.57) vs. 750 (0.89)	84 (0.36) vs. 210 (0.85)	272 (0.49) vs. 375 (0.55)	77 (0.40) vs. 85 (0.36)	85 (0.36) vs. 115 (0.48)
	Hazard Ratio (ICH)	0.56 [0.48-0.65]	0.63 [0.56-0.71]	0.43 [0.33-0.55]	0.86 [0.73-1.00]	1.04 [0.76-1.42]	0.75 [0.57-1.00]
	*Outcome***	*apixaban (n=100,977) vs. warfarin (n=100,977)*	*rivaroxaban (n=125,068) vs. warfarin (n=125,068)*	*dabigatran (n=36,990) vs. warfarin (n=36,990)*	*apixaban vs. (n=107,236) rivaroxaban (n=107,236)*	*apixaban vs. (n=37,314) dabigatran (n=37,724)*	*dabigatran vs. (n=37,724) rivaroxaban (n=37,724)*
Mortality	Death	2,730 (6.81) vs. 5,036 (9.63)	4,343 (7.11) vs. 5,867 (9.08)	932 (5.68) vs. 1,414 (8.15)	2,692 (6.56) vs. 3,704 (7.23)	762 (5.79) vs. 932 (5.69)	933 (5.69) vs. 1,050 (6.39)
	Hazard Ratio	0.65 [0.62-0.68]	0.78 [0.75-0.81]	0.70 [0.64-0.76]	0.84 [0.80-0.89]	0.97 [0.88-1.06]	0.89 [0.82-0.97]

Numbers of events (Rates per 100-person-years)
**Propensity score-matched cohorts*
***CMS Medicare Population among propensity score-matched cohorts (data subset)*
Adapted from ARISOTOPHANES Figure 2 and Supplemental Tables XII and XIII.
Numbers of events (Rates per 100-person-years)

DOAC therapy.[1] This recommendation is extrapolated from the RE-ALIGN trial comparing dabigatran to warfarin in patients with mechanical heart valves.[25] The study was stopped early as dabigatran was shown to have increased risk of stroke and mortality.

AF guidelines consider apixaban, the DOAC with lowest renal elimination at 27%, to be a reasonable alternative (Level 2b/B recommendation; weak benefit moderate qualify of evidence) to warfarin for the patient with renal impairment as well as end-stage renal disease (ESRD) and dialysis.[1,7,26] Apixaban has an FDA approval for use in patients with concomitant AF and ESRD and/or dialysis from a small, single-dosed single-dosed pharmacokinetic (PK) study of 8 patients.[27] Notably, apixaban is not dialyzable either via peritoneal or hemodialysis nor requires dose adjustments in hemodialysis.[7] Additional retrospective data from 2,300 dialysis patients on apixaban compared to 25,000 warfarin patients demonstrated lower overall bleeding rates with apixaban (HR 0.71, 0.59-0.87, P< 0.001), but rates of stroke and embolism (HR 0.88; 0.69-1.12) were not statistically significantly lower. However, half of patients in the apixaban arm were prescribed the lower 2.5mg BID dose in comparison to the standard 5mg BID dose.[7,26] Pending prospective RCTs to evaluate this include RENAL-AF (Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients with Atrial Fibrillation), which will randomize patients to apixaban 5mg BID or warfarin, and the AXADIA study (Compare Apixaban and Vitamin-K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease), which will randomize patients to apixaban 2.5 mg BID versus a vitamin K antagonist.[28]

Similarly, rivaroxaban also has a small, single-dose PK study of 32 patients, 24 of whom had varying degrees of renal function but were not on renal replacement therapies, who received one 10 mg dose of rivaroxaban. PK data showed a decrease in rivaroxaban clearance but only moderately impactful even in those with creatinine clearance less than 30 mL/min.[29] Despite this PK data, AF Guidelines refer to the use of rivaroxaban (as well as dabigatran and edoxaban) in end-stage CKD or dialysis to be a Level 3/C-EO recommendation (data lacks to prove that benefit exceeds risk based on expert opinion). Rivaroxaban, dabigatran, and edoxaban can, however, be considered in mild to moderate renal impairment per the package labeling and is a Level 2b/B recommendation in AF Guidelines (weak benefits outweigh risks with moderate quality evidence).[1,6,8,9]

TABLE 5. Comparison of Prospective DOAC Acute VTE Trials[34-39]

	AMPLIFY (apixaban)	EINSTEIN-DVT, EINSTEIN-PE (rivaroxaban)	RE-COVER, RE-COVER II (dabigatran)	HOKUSAI-VTE (edoxaban)
Efficacy outcomes for acute VTE treatment				
Recurrent VTE or VTE-related death	Non-inferior	Non-inferior	Non-inferior	Non-inferior
Safety outcomes for acute VTE treatment				
First major or clinically relevant non-major bleeding event	**Superior**	Non-inferior	**Superior**	**Superior**

VTE = venous thromboembolism

While there are no prospective studies comparing DOACs in head-to-head randomized controlled trials (RCTs), the ARISTOPHANES (Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients) study is one of the largest observational claims-based studies pooling DOAC use in over 280,000 patients with atrial fibrillation.[30] Stroke, systemic embolism, and major bleeding were efficacy and safety end points and results are in Table 4.

Most patients included in ARISTOPHANES were on either warfarin (n=167,413) or rivaroxaban (n=153,002), followed by apixaban (n=108,852), and dabigatran (n=37,724). The patient demographics, comorbidities, CHA_2DS_2VASc scores, HAS-BLED scores were balanced between study arms. Approximately 75%-85% of patients prescribed a DOAC were on full dose therapy (77.5% apixaban, 84.6% dabigatran, and 72.1% rivaroxaban) with the remainder of patients on lower dose therapy. Patients prescribed lower dose therapy corresponded well with the rates of reported renal disease (23%, 16%, and 20% with apixaban, dabigatran and rivaroxaban respectively).

The ARISTOPHANES study, while observational, cumulatively triples the number of patients studied in original DOAC AF RCTs. ARISTOPHANES further supports original DOAC study findings that apixaban and dabigatran are both superior to warfarin in both efficacy and bleeding with the data favoring apixaban. In ARISTOPHANES, rivaroxaban demonstrates improved efficacy outcomes in comparison to ROCKET-AF in which rivaroxaban performed about similarly (non-inferior) to warfarin. The bleeding rate with rivaroxaban use, while similar to warfarin, appears to be higher than when compared either apixaban or dabigatran. Since data from ARISTOPHANES is observational, caution should be used when drawing conclusions between DOACs. Current DOAC to DOAC prospective RCTs in process include DARING-AF (Comparison of Efficacy and Safety among Dabigatran, Rivaroxaban, and Apixaban in Nonvalvular Atrial Fibrillation) and DANNOAC-AF (The Danish Non-Vitamin K Antagonist Oral Anticoagulation Study: A Cluster Randomized Study Comparing Safety and Efficacy of Edoxaban, Apixaban, Rivaroxaban and Dabigatran for Oral Anticoagulation in Atrial Fibrillation).[31,32]

Venous Thromboembolism

VTE encompasses pulmonary embolism (PE) and deep vein thrombosis (DVT). In the United States, up to 900,000 people are affected by VTE events annually.[33] It is fatal for 10%-30% of people within one month of diagnosis.[33] Prompt initiation of an anticoagulant is crucial to prevent VTE recurrence and VTE-related death. While warfarin has been the oral anticoagulant treatment for VTE for decades, DOACs have now emerged as a preferred anticoagulant for eligible patients.[2,3]

Two national organizations have

released recent guidelines for management of VTE. In 2020, the American Society of Hematologists (ASH) published "American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism."[2] In 2021, CHEST updated their guideline "Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report."[3] Key guidance statements and recommendations pertaining to DOACs in non-surgical, non-cancer patients are reviewed in this article.

Initiation and Treatment Phase

The approach to treatment of VTE is separated into two phases. The initial phase refers to the time period where anticoagulants are given after VTE diagnosis and lasts up to 5-21 days, based on which anticoagulant is selected.[2,3] The treatment phase lasts for a minimum of 3 months following the initial phase.[2,3] Apixaban and rivaroxaban can be used as monotherapy choices in both the initial and treatment phase.[6,7] Edoxaban and dabigatran require a parenteral anticoagulant for 5-10 days prior to starting either agent.[5,8] After the initial treatment with a parenteral anticoagulant is completed, edoxaban or dabigatran can be used as monotherapy for the treatment phase.[5,8] It is crucial that the correct DOAC doses are used for proper treatment of VTE (Figure 3).

Direct comparisons of DOACs for VTE is limited. Some factors in choosing a DOAC may be dependent on cost, renal function, once vs twice daily dosing, age, drug interactions and/or requirement for lead-in parenteral anticoagulation. The CHEST guidelines suggest that apixaban may offer a lower bleeding risk than other DOACs but do not make a formal recommendation on DOAC preference.[3] ASH guidelines state: "For patients with DVT and/or PE, the ASH guideline panel does not suggest 1 DOAC over another (conditional recommendation based on very low certainty in the evidence of comparative effects)."[2]

Key trials to evaluate the safety and efficacy of DOACs for use in VTE include RE-COVER/RE-COVER II (dabigatran), AMPLIFY (apixaban), EINSTEIN-DVT/EINSTEIN-PE (rivaroxaban), and HOKUSAI-VTE (edoxaban).[34-39] The overall findings of these studies are listed in Table 5.

FIGURE 3. DOAC Dosing[5-9]

	apixaban	*rivaroxaban*	*dabigatran*	*edoxaban*
Treatment of acute DVT and/or PE	10mg BID x 7 days then 5mg BID^	15mg BID x 21 days then 20mg daily with largest meal of day^	150mg BID AFTER 5-10 days of parenteral lead-in^	60mg daily AFTER 5-10 days of parenteral lead-in *^
Reduction of risk of recurrent DVT and/or PE	2.5mg BID after 6 months of initial treatment^	10mg daily after 6 months of initial treatment^	150mg BID after initial treatment^	Not FDA approved for this indication
Atrial Fibrillation	5mg BID 2.5mg BID if 2 of the following: • age ≥80 • weight < 60 kg • SCr ≥ 1.5	20mg daily with largest meal of day*^	150mg BID*^	60mg daily*^+

**requires renal dosing adjustment for CrCl 15-50 mL/min, refer to PI for details*
^avoid use in severe renal impairment CrCl <30 mL/min
+ avoid use if CrCl > 95 mL/min
Abbreviations: BID (twice daily), DVT (deep vein thrombosis), kg (kilogram), PE (pulmonary embolism), SCr (serum creatinine)
Adapted and reproduced with permission from The 2021 DOAC Playbook - Anticoagulation Forum©

Both 2020 ASH and 2021 CHEST VTE guidelines favor DOACs over VKA in the treatment phase:

- ASH: "For patients with DVT and/or PE, the ASH guideline panel suggests using direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) (conditional recommendation based on moderate certainty in the evidence of effects). Remarks: This recommendation may not apply to certain subgroups of patients, such as those with renal insufficiency (creatinine clearance, 30 mL/min), moderate to severe liver disease, or antiphospholipid syndrome".[2]
- CHEST: "In patients with VTE (DVT of the leg or PE) we recommend apixaban, dabigatran, edoxaban, or rivaroxaban over vitamin K antagonist (VKA) as treatment-phase (first 3 months) anticoagulant therapy (strong recommendation, moderate-certainty evidence)".[3] The 2021 CHEST update increased the previous GRADE of recommendation from weak recommendation, moderate-quality evidence to strong recommendation, moderate-quality evidence.

Extended Treatment Phase

In patients with an unprovoked VTE event, estimates of VTE recurrence after discontinuation of anticoagulation is 10% after one year, 25% after five years and 36% after 10 years.[40] An individualized risk/benefit analysis of continuing anticoagulation should be performed after the treatment phase and periodically thereafter. Aspects to consider include risk factors for recurrent VTE (transient or persistent), age, renal/liver function, past bleeding history, current bleeding risks and patient preference.[40]

If the decision is made to continue anticoagulation after treatment phase dosing, DOACs that have been evaluated for secondary prevention include apixaban, dabigatran, and rivaroxaban. Edoxaban is not FDA-approved for extended treatment. The AMPLIFY-EXT (apixaban), RE-SONATE (dabigatran) and EINSTEIN-EXTENSION (rivaroxaban) trials demonstrated superiority in preventing symptomatic recurrent DVT compared to placebo without a significant increase in major bleeding.[41-43] When compared to warfarin, the RE-MEDY (dabigatran) trial was noninferior to warfarin in preventing recurrent DVT with significantly lower rates of bleeding.[42]

If anticoagulation is extended, the anticoagulant dose should be re-evaluated. Dabigatran dosing remains the same. Apixaban can be reduced from 5mg twice daily to 2.5mg twice daily based on the

AMPLIFY- EXT trial.[41] Rivaroxaban can be reduced from 20mg once daily with food to 10mg daily with or without food based on the EINSTEIN-CHOICE trial.[44] However, the patients in those two studies did not have strong indications for indefinite anticoagulation and were not designed or powered to evaluate noninferiority of efficacy and superiority of safety with reduced dose DOAC compared to full dose DOAC.

Both ASH and CHEST VTE guidelines address reduced-dose DOAC based on available evidence:

- ASH: "For patients with DVT and/or PE who have completed primary treatment and will continue with a DOAC for secondary prevention, the ASH guideline panel suggests using a standard-dose DOAC or a lower-dose DOAC (conditional recommendation based on moderate certainty in the evidence of effects)".[2]
- CHEST: "In patients offered extended-phase anticoagulation, we suggest the use of reduced-dose apixaban or rivaroxaban over full-dose apixaban or rivaroxaban (weak recommendation, very low certainty evidence)."[3]

Importantly, the RENOVE study (REduced Dose Versus Full-dose of Direct Oral Anticoagulant After uNprOvoked Venous thromboembolism) is currently underway with expected completion date of October 2023.[45] It is a randomized, parallel arm, controlled trial with an estimate 2200 participants. Their hypothesis is "After VTE at high risk of recurrence initially treated during 6 (-15 days) to 24 (+ 3 months) uninterrupted months, a reduced dose of DOAC will be non-inferior to a full dose of DOAC in terms of recurrent VTE during extended anticoagulation phase." The results of this study will give more insight into whether DOAC doses should be reduced or not during extended phase anticoagulation treatment.

Barriers to DOAC Use

The decision to start anticoagulation and the selection of anticoagulant should ideally be accomplished through shared decision-making with the patient.[1,46,47] This approach is more collaborative and conversational in comparison to past prescriptive practices. While guidelines, studies, and data favor a DOAC over VKA for most patients with VTE or AF, there can be potential barriers preventing DOAC use. Lack of provider clinical knowledge or perceptions of OAC options, along with financial challenges, are some of the top concerns.[48]

Prescription claims data can give insight into OAC prescribing trends. The most recent Medicare Provider Utilization and Payment Data from 2013-2018 was retrospectively analyzed to evaluate OAC prescribing in the United States.[49] Over the study period, warfarin prescription volume decreased from 85.9% of all anticoagulant prescriptions to 42.7%. Conversely, DOAC prescription volume increased from 14.1% of all anticoagulant prescriptions in 2013 to 57.3% in 2018. There were significant differences in prescribing trends based on specialty. Among anticoagulant prescribers prescribing only warfarin in 2018, 1.6% were cardiologists, 12.6% were internal medicine physicians, 20.0% were family medicine physicians and 28.2% were advance practice clinicians.

DOAC availability can improve patients' prior OAC concerns based on when warfarin was the only option. Patients with a needle phobia may now only need annual or bi-annual laboratory testing.[1,3,9] This less frequent lab monitoring may also assist patients with transportation or access concerns.

The largest issue most patients and providers face when considering OAC is cost. DOACs are oftentimes cost prohibitive to patients when directly compared to warfarin. Patients with AF are likely to require indefinite anticoagulation, whereas for initial episodes of VTE, higher drug costs for a fixed 3-to-6-month period may be easier to afford. Furthermore, DOACs are subject to Medicare's coverage gap (i.e. donut hole) as well as annual deductible that make DOAC costs at certain parts of the year much higher than at other times.[50] For example, a DOAC copay may be $480 in January of a calendar year as subject to the deductible, but then as much as 10 times lower (i.e. $47 per month) during the initial coverage phase. The improved bleeding profiles with equal or better efficacy of DOACs are also indirect opportunity costs that are difficult to quantify, particularly for older patients who may experience fixed incomes. Taking into consideration medical bills for lab draws may also improve the conversation when financially comparing OAC options.

Pharmacists have extensive experience with prescription drug coverage/costs in addition to the training and background in pharmacotherapy to differentiate the DOAC drug class from VKAs (Table 1). Manufacturer sponsored copayment assistance cards have improved access to DOACs for many privately insured patients,

FIGURE 4. DOAC PAP Financial Screening Tool*

1. Calculate household size (according to taxes)
2. Approximate gross annual income for household (according to taxes)
3. Gross Income must be ≤ 300% FPL to quality
4. If insured by Medicare Part D, calculate applicant's individual OOP (see below)
5. Submit application for PAP[56-58]

2022 Federal Poverty Level (FPL)	
Household Size	*300%*
1	$40,770
2	$54,930
3	$69,090
4	$83,250
5	$97,410
6	$111,570

**For underinsured or uninsured patients only. Medicare Part D patients are eligible. Wisconsin Medicaid/Badgercare patients are excluded as DOACs are a covered benefit.[59] Patients with commercial insurance programs with high copays should be referred to manufacturer sponsored copay assistance.[51-54]*

Drug PAP	*Program*	*Qualifying Income*	*OOP for Medicare Part D***
Direct Oral Anticoagulants			
ELIQUIS®	BMS	< 300% FPL	3%
PRADAXA®	BOEHRINGER	< 300% FPL	0%
XARELTO®	J & J	< 300% FPL	4%
SAVAYSA®	NO PAP	NO PAP	NO PAP

**OOP = Out of Pocket Spending. OOP is applicable to patients with Medicare Part D coverage only. The OOP is a total percentage of gross income spent in the calendar year on prescription medications for applicant applying for PAP. Patient must submit proof of OOP for PAP sponsored drug to be issued for remainder of calendar year.[56-58]*

but patients who are uninsured or who have coverage under Medicare or Medicaid do not qualify.[51-54] The Janssen Select Program is the only manufacturer sponsored program Medicare Part D patients are eligible for without a financial screening. Janssen Select discounts rivaroxaban for as low as $80 per month to patients with any prescription coverage (including Medicare Part D and any income) from April to December of each calendar year.[55]

Another underutilized financial resource is the availability of manufacturer-sponsored Patient Assistance Programs (PAPs).[56-58] Drug manufacturers offer these programs for patients who are prescribed a DOAC and have a gross income less than 300% the Federal Poverty Level (Figure 4: DOAC PAP Financial Screening Tool). Patients with Medicare Part D coverage wanting access to the PAP for Xarelto® or Eliquis® must meet 3%-4% annual out-of-pocket spending on prescription medications before they will be issued free drug. The PAP applications require both provider and patient signatures and must be submitted annually with proof of income and thus can add complexity and/or additional work to clinical staff.

Conclusion

As pharmacists and healthcare professionals, creating patient relationships allows two-way conversations with shared decision-making of OAC options. While cost can be a common and significant barrier to DOAC use, a deeper dive into financial resources available to patients could improve both overall OAC use as well as facilitate converting patients from a VKA to a DOAC—the preferred anticoagulant for AF and VTE.

Christi Albert, Kristina Yokes, and Anne Rose are Clinical Pharmacists at UW Health Anticoagulation Clinic in Madison, WI.

Disclosure: The author(s) declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria."

References

1. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration with the Society of Thoracic Surgeons. *Circulation*. 2019;140(2):e125-e151. doi: 10.1161/CIR.0000000000000665
2. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693-4738. doi: 10.1182/bloodadvances.2020001830
3. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and Expert Panel Report. *Chest.* 2021;160(6):e545-e608. doi: 10.1016/j.chest.2021.07.055
4. COUMADIN® (warfarin sodium) tablets, for oral use. Full prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; 2017.
5. PRADAXA® (dabigatran etexilate mesylate) capsules for oral use. Full prescribing information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2021.
6. XARELTO® (rivaroxaban) tablets, for oral use. Full prescribing information. Titusville, NJ: Janssen Pharmaceutical, Inc; 2021.
7. ELIQUIS® (apixaban) tablets for oral use. Full prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; 2021.
8. SAVAYSA® (edoxaban) tablets for oral use. Full prescribing information. Parsippany, NJ: Daiichi Sankyo, Inc; 2021.
9. Anticoagulation Forum. Direct Oral Anticoagulant: DOAC Playbook. Updated July 2021. Accessed May 28, 2022. https://acforum-excellence.org/Resource-Center/downloads/DOAC%20Playbook%20_07-2021.pdf
10. Vallakati A, Lewis WR. Underuse of anticoagulation in patients with atrial fibrillation. *Postgrad Med*. 2016;128(2):191-200. doi: 10.1080/00325481.2016.1132939
11. Szucs TD, Bramkamp M. Pharmacoeconomics of anticoagulation therapy for stroke prevention in atrial fibrillation: a review. *J Thromb Haemost.* 2006;4(6):1180-1185. doi: 10.1111/j.1538-7836.2006.01890.x
12. McDermott, A. Types of atrial fibrillation: what you need to know. Healthline. Updated June9th 2020. Accessed June 1, 2022. https://www.healthline.com/health/atrial-fibrillation/types-of-atrial-fibrillation#permanent-afib
13. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33(12):1500-1510. doi: 10.1093/eurheartj/ehr488
14. O'Brien EC, Kim S, Hess PL, et al. Effect of the 2014 atrial fibrillation guideline revisions on the proportion of patients recommended for oral anticoagulation. *JAMA Intern Med.* 2015;175(5):848-850. doi: 10.1001/jamainternmed.2015.13
15. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med*. 2010;123(7):638-645. doi: 10.1016/j.amjmed.2009.11.025
16. Baczek VL, Chen WT, Kluger J, Coleman CI. Predictors of warfarin use in atrial fibrillation in the United States: a systematic review and meta-analysis. *BMC Fam Pract.* 2012;13:5. doi: 10.1186/1471-2296-13-5
17. Shoeb M, Fang MC. Assessing bleeding risk in patients taking anticoagulants. *J Thromb Thrombolysis.* 2013;35(3):312-319. doi: 10.1007/s11239-013-0899-7
18. Fang MC, Go AS, Chang Y, et al. Warfarin discontinuation after starting warfarin for atrial fibrillation (ATRIA). *Circ Cardiovasc Qual Outcomes*. 2010;3(6):624-631. doi: 10.1161/CIRCOUTCOMES.110.937680
19. O'Brien EC, Simon DN, Allen LA, et al. Reasons for warfarin discontinuation in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J.* 2014;168(4):487-494. doi: 10.1016/j.ahj.2014.07.002
20. Piccini JP, Xu H, Cox M, et al. Adherence to guideline-directed stroke prevention therapy for atrial fibrillation is achievable. *Circulation.* 2019;139(12):1497-1506. doi: 10.1161/CIRCULATIONAHA.118.035909
21. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992. doi: 10.1056/NEJMoa1107039
22. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369(22):2093-2104. doi: 10.1056/NEJMoa1310907
23. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-1151. doi: 10.1056/NEJMoa0905561
24. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation (ROCKET-AF). *N Engl J Med.* 2011;365(10):883-891. doi: 10.1056/NEJMoa1009638
25. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med.* 2013;369(13):1206-1214. doi: 10.1056/NEJMoa1300615
26. Siontis KC, Zhang X, Eckard A, et al. Outcomes Associated with Apixaban Use in Patients with End-Stage Kidney Disease and Atrial Fibrillation in the United States *Circulation*. 2018;138(15):1519-1529. doi: 10.1161/CIRCULATIONAHA.118.035418
27. Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. *J Clin Pharmacol.* 2016;56(5):628-636. doi: 10.1002/jcph.628
28. Hylek EM. Apixaban for End-Stage Kidney Disease. *Circulation.* 2018;138(15):1534-1536. doi: 10.1161/CIRCULATIONAHA.118.036449
29. Kubitza D, Becka M, Mueck W, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br J Clin Pharmacol*. 2010;70(5):703-712. doi: 10.1111/j.1365-2125.2010.03753.x
30. Lip GYH, Keshishian A, Li X, et al. Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. *Stroke*. 2018;49(12):2933-2944. doi: 10.1161/STROKEAHA.118.020232
31. Comparison of Efficacy and Safety Among Dabigatran, Rivaroxaban, and Apixaban in Non-Valvular Atrial Fibrillation (DARING-

AF). ClinicalTrials.gov. Updated February 17th 2016. Accessed June 1st 2022. https://clinicaltrials.gov/ct2/show/NCT02666157
32. The Danish Non-vitamin K Antagonist Orla Anticoagulation Study in Patients with Atrial Fibrillation (DANNOAC-AF). Updated August 7th 2018. Accessed June 1st 2022. https://clinicaltrials.gov/ct2/show/NCT03129490
33. Venous Thromboembolism (Blood Clots). Centers for Disease Control and Prevention. Updated April 25, 2022. Accessed May 28, 2022. https://www.cdc.gov/ncbddd/dvt/data.html
34. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510. doi: 10.1056/NEJMoa1007903
35. EINSTEIN–PE Investigators, Büller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-1297. doi: 10.1056/NEJMoa1113572
36. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808. doi: 10.1056/NEJMoa1302507
37. Hokusai-VTE Investigators, Büller HR, Décousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism [published correction appears in *N Engl J Med.* 2014 Jan 23;370(4):390]. N Engl J Med. 2013;369(15):1406-1415. doi: 10.1056/NEJMoa1306638
38. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med.* 2009;361(24):2342-2352. doi: 10.1056/NEJMoa0906598
39. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129(7):764-772. doi: 10.1161/CIRCULATIONAHA.113.004450
40. Khan F, Rahman A, Carrier M, et al. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. *BMJ*. 2019;366:l4363. doi: 10.1136/bmj.l4363
41. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med.* 2013;368(8):699-708. doi: 10.1056/NEJMoa1207541
42. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med.* 2013;368(8):709-718. doi:10.1056/NEJMoa1113697
43. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510. doi:10.1056/NEJMoa1007903
44. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376(13):1211-1222. doi: 10.1056/NEJMoa1700518
45. REduced Dose Versus Full-dose of Direct Oral Anticoagulant After uNprOvoked Venous thromboembolism (RENOVE). ClinicalTrials.gov. Updated April 22, 2022. Accessed May 28, 2022. https://clinicaltrials.gov/ct2/show/NCT03285438
46. Frost H, Campbell P, Maxwell M, et al. Effectiveness of motivational interviewing on adult behavior change in health and social care settings: a systematic review of reviews. *PLoS One*. 2018;13(10):e0204890. doi: 10.1371/journal.pone.0204890
47. Bradshaw J, Siddiqui N, Greenfield D, Sharma A. Kindness, listening, and connection: patient and clinician key requirements for emotional support in chronic and complex care. *J Patient Exp*. 2022;9:1-7. doi: 10.1177/23743735221092627
48. Barnes GD, Acosta J, Graves C, et al. Barriers to integrating direct oral anticoagulants into anticoagulation clinic care: a mixed-methods study. Res Pract Thromb Haemost. 2018;3(1):79-84. doi: 10.1002/rth2.12157
49. Wheelock KM, Ross JS, Murugiah K, Lin Z, Krumholz HM, Khera R. clinician trends in prescribing direct oral anticoagulants for US Medicare beneficiaries. *JAMA Netw Open.* 2021;4(12):e2137288. doi: 10.1001/jamanetworkopen.2021.37288
50. Pharmacist Quick 2022 Medicare Part D Reference. National Community Pharmacists Association (NCPA) Guide. Accessed June 1, 2022. https://ncpa.org/sites/default/files/2021-10/quick-ref-guide-medicare-part-d-2022.pdf
51. Eliquis® 360 Support. Bristol-Myers Squibb Company. Updated 2021. Accessed June 1, 2022 Savings And Support | Rx ELIQUIS® (apixaban) (bmscustomerconnect.com)
52. Janssen CarePath Trial Offer Card for Xarelto®. Janssen Pharmaceuticals, Inc. Updated December 2021. Accessed June 1, 2022. Trial Offer Card - XARELTO (trialcard.com)
53. Janssen CarePath Savings Program $10 Copay Card for Xarelto®. Janssen Pharmaceuticals, Inc. Updated March 2022. Accessed June 1, 2022. Savings Program Overview – XARELTO (janssencarepath.com)
54. Savaysa Support. Daiichi Sankyo, Inc. Updated August 2020. Accessed June 1, 2022. Support+™ Program & Resources | SAVAYSA® (edoxaban)
55. Janssen Select Affordability Program for Xarelto®. Janssen Pharmaceuticals, Inc. Updated March 2022. Accessed June 1, 2022. Janssen Select Affordability Program for XARELTO® (rivaroxaban)
56. Bristol Myers Squibb Patient Assistance Foundation (BMSPAF) Eliquis® Application. Updated August 2021. Accessed June 1, 2022. https://www.needymeds.org/papforms/bmspae0042.pdf
57. Johnson & Johnson Foundation, Inc. Xarelto® Patient Assistance Program Application. Updated January 2022. Accessed June 1, 2022. https://www.needymeds.org/papforms/jpapae0996.pdf
58. Boehringer Ingelheim Cares Foundation. Patient Assistance Program Application. Updated May 17th 2022. Accessed June 1, 2022. https://www.needymeds.org/papforms/bicpae3360.pdf
59. Wisconsin Medicaid Preferred Drug List Quick Reference. Forward Health, Wisconsin Serving You. Updated June 1st 2022. Accessed June 1, 2022. https://www.forwardhealth.wi.gov/wiportal/content/provider/medicaid/pharmacy/resources.htm.spage#

Assessment Questions

1. When selecting an oral anticoagulant for a patient, which of the following should NOT be taken into consideration?
   a. Medication copay
   b. Renal function
   c. Reversal agents
   d. Drug interactions

2. DOACs have which of the following advantages over VKAs?
   a. Limited dietary interactions
   b. Preferred anticoagulant for AF and VTE
   c. Rapid onset
   d. All of the above

3. Which is NOT a contraindication for use of a DOAC?
   a. Triple positive antiphospholipid antibody syndrome
   b. Creatinine clearance of 20 mL/min
   c. Mechanical heart valve replacement
   d. Concurrent use of rifampin

4. **True or False:** DOACs can be used in patients with mechanical heart valves or moderate to severe mitral stenosis as long as they have underlying atrial fibrillation.
   a. True
   b. False

5. **True or False:** Edoxaban (Savaysa®) would be a reasonable DOAC to continue for a patient with AF while hospitalized with anuric AKI requiring dialysis if they had been established on it as an outpatient before hospital admission.
   a. True
   b. False

6. **True or False:** A patient with AF should not take oral anticoagulation if a prescriber has not documented the CHA2DSVASC2 score in the medical record.
   a. True
   b. False

7. In a patient with a new PE, which anticoagulant can be used for initial treatment without low molecular weight heparin (LMWH)?
   a. Warfarin
   b. Dabigatran
   c. Edoxaban
   d. Apixaban

8. Which DOAC is NOT approved for extended treatment of VTE?
   a. Apixaban
   b. Dabigatran
   c. Edoxaban
   d. Rivaroxaban

9. A patient with Medicare Part D has an annual income of $42,000 with a

household size of two people. She has currently spent 3% of her income on out-of-pocket Medicare Part D expenses. Which medication's PAP programs could she apply for?
a. Eliquis® and Pradaxa®
b. Eliquis® and Xarelto®
c. Xarelto® and Pradaxa®
d. Pradaxa® and Xarelto®

10. A thirty-year old patient is diagnosed with a new DVT. He has commercial drug insurance with a tier 2 DOAC copay of $50/month. What resource would likely provide him cost savings?
a. Manufacturer patient assistance programs
b. Manufacturer copay cards
c. Switching pharmacies
d. Discount prescription drug cards

11. Did the activity meet the stated learning objectives? (if you answer no, please email sarahs@pswi.org to explain)
a. Yes
b. No

12. On a scale of 1 – 10 (1-no impact; 10-strong impact), please rate how this program will impact the medication therapy management outcomes or safety of your patients.

13. On a scale of 1 – 10 (1-did not enhance; 10-greatly enhanced), please rate how this program enhanced your competence in the clinical areas covered.

14. On a scale of 1 – 10 (1-did not help; 10-great help), please rate how this program helped to build your management and leadership skills.

15. How useful was the educational material?
a. Very useful
b. Somewhat useful
c. Not useful

16. How effective were the learning methods used for this activity?
a. Very effective
b. Somewhat effective
c. Not effective

17. Learning assessment questions were appropriate.
a. Yes
b. No

18. Were the authors free from bias?
a. Yes
b. No

19. If you answered "no" to question 18, please comment (email info@pswi.org).

20. Please indicate the amount of time it took you to read the article and complete the assessment questions.

CE FOR **PHARMACISTS**

Submit Your CE Online!

www.pswi.org/Education/Journal-CE

Continuing Education Credit Information

The Pharmacy Society of Wisconsin is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. Continuing education credit can be earned by completing the self assessment questions. Questions may be completed online at www.pswi.org or by mailing completed answer form to PSW, 701 Heartland Trail, Madison, WI 53717. Participants receiving a score of 70% or better will be granted 1hour (0.1 CEU) credit through CPE Monitor within 60 day of quiz completion. Accurate birth date (MMDD) and CPE Monitor ID must be provided in order to receive this credit as required by ACPE.

This CE offering is offered free-of-charge to all PSW members. Nonmembers are charged $20 for each exam submitted to cover administrative costs.

Quiz Answer Form

circle one answer per question

1) a b c d
2) a b c d
3) a b
4) a b
5) a b
6) a b
7) a b c d
8) a b c d
9) a b c d
10) a b c d
11) a b
12)_____
13)_____
14)_____
15) a b c
16) a b c
17) a b
18) a b
19)_____
20)_____

July/August 2022
The X-Factor: Overcoming DOAC Barriers in OAC Eligible Patients
ACPE Universal Activity Number: 0175-0000-22-108-H04-P
Target Audience: Pharmacists
Activity Type: Knowledge-based
Release Date: July 1, 2022
(No longer valid for CE credit after July 1, 2025)

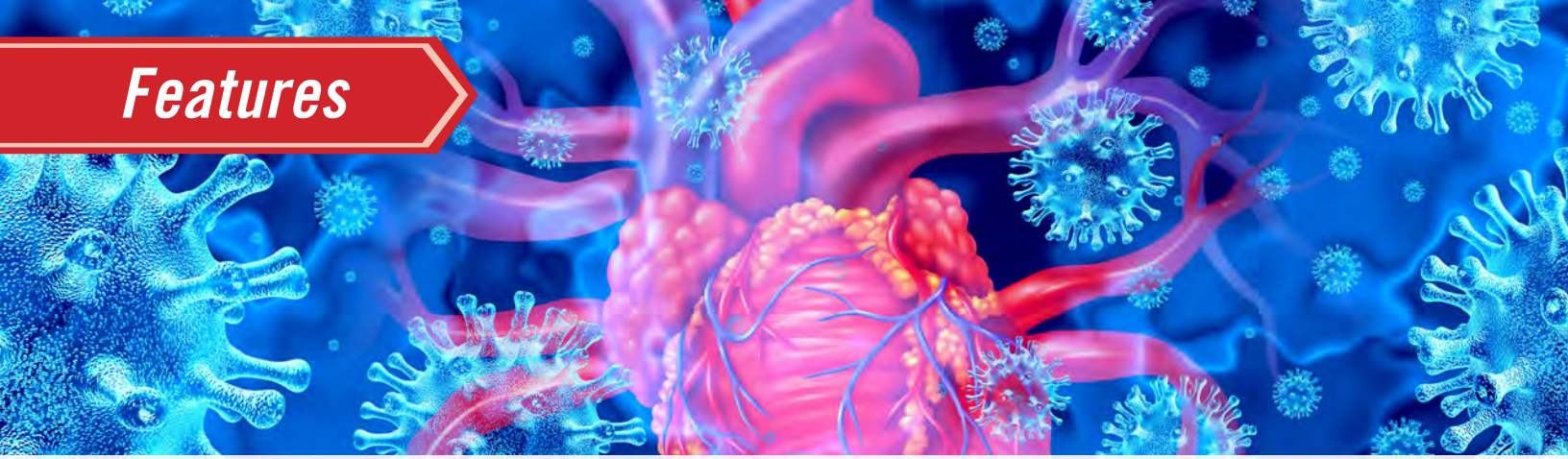
Name_____ Designation (RPh, PharmD, etc.) _____

CPE Monitor # _____ DOB (MMDDYY) _____

Preferred Mailing Address_____

City _____ State_____ Zip _____

Is this your home ☐ or work ☐ address?



ID CORNER
Viral Myocarditis

by Ami Leigh Schmidt, 2023 PharmD Candidate, Etan Maistelman, 2023 PharmD Candidate, Kristen Bunnell, PharmD, BCCCP, BCIDP

Myocarditis, or inflammation of the myocardium of the heart, can be precipitated by a variety of infectious and noninfectious etiologies. Viruses are the most common cause of infectious myocarditis, a fact that has been highlighted in recent years by reports of patients who developed myocarditis following COVID-19 infection and vaccination. The objective of this manuscript is to review the epidemiology and treatment of viral myocarditis, with a focus on COVID-19.

Epidemiology

The global prevalence of myocarditis in 2017 was estimated to be 1.8 million cases, translating to approximately 15 cases per 100,000 people in North America.[1] The incidence in children is estimated to be 0.26-2.0 cases per 100,000 people, with the highest incidence in infancy and adolescence.[2]

Myocarditis is most commonly caused by viruses, but bacteria, fungi, and even parasites can play a role, especially in developing countries. In addition, noninfectious etiologies must be considered, which may be toxin-, medication-, or immune-mediated (Table 1).[3,4]

Clinical Presentation

Patients typically report cardiac symptoms of chest pain, dyspnea, or palpitations.[3-5] In cohort studies of patients with acute myocarditis, chest pain is a presenting symptom in 85%-90% of patients.[6,7] Patients may also endorse nonspecific symptoms, such as fatigue, fever, shortness of breath, myalgia, nausea, vomiting, or poor appetite. Most patients with myocarditis will recover fully from the disease, but approximately 20% of patients will develop inflammatory dilated cardiomyopathy.[8] Advanced cardiomyopathy from myocarditis may lead to left ventricular dysfunction and heart failure, ventricular arrythmias, or cardiogenic shock (fulminant myocarditis).[3] Myocarditis is thought to be an inciting factor in up to 10% of sudden cardiac deaths in children and young adults, and up to 20% of cases of sudden infant death syndrome.[5,9,10]

Diagnosis

Viral myocarditis is typically a disease of exclusion from other inflammatory and cardiovascular conditions. Clinicians can use the Sagar criteria to classify myocarditis as possible, probable, or definite based on clinical symptoms, electrocardiogram (EKG) and echocardiogram findings, and cardiac enzymes.[4] In patients with myocarditis, labs show elevated inflammatory markers, troponin, and natriuretic peptides. A patient's EKG may have ST-segment elevation and wide QRS complex.[2,5] If the patient has progressed to cardiomyopathy, an echocardiogram will show left ventricle dysfunction or wall motion abnormalities. The gold standard diagnostic approach to myocarditis has historically been from histopathologic findings from an endomyocardial biopsy (EMB) of the right ventricular septal wall. Unfortunately, this procedure is invasive, and it is not always done in practice.[2] Experts suggest that EMB should be prioritized in patients with acute cardiomyopathy requiring inotropic agents or mechanical circulatory support, or acute arrythmias without clear cause.[5] Biopsy is the only way to determine the specific subtype of myocarditis, which has an implication for treatment approaches.[8] Patients who present with suspected myocarditis of a less severe magnitude may be candidates for cardiac magnetic resonance imaging (CMR), which has been shown to be highly sensitive and specific for the diagnosis of myocarditis in combination with lab and clinical data.[11] The American College of Cardiology Expert Consensus Decision Pathway defines myocarditis as: (1) the presence of cardiac symptoms such as chest pain and dyspnea, (2) an elevated cardiac troponin, and (3) abnormal EKG or echocardiogram, CMR with characteristic findings, and/or histopathologic confirmation on EMB.[12]

Pathophysiology

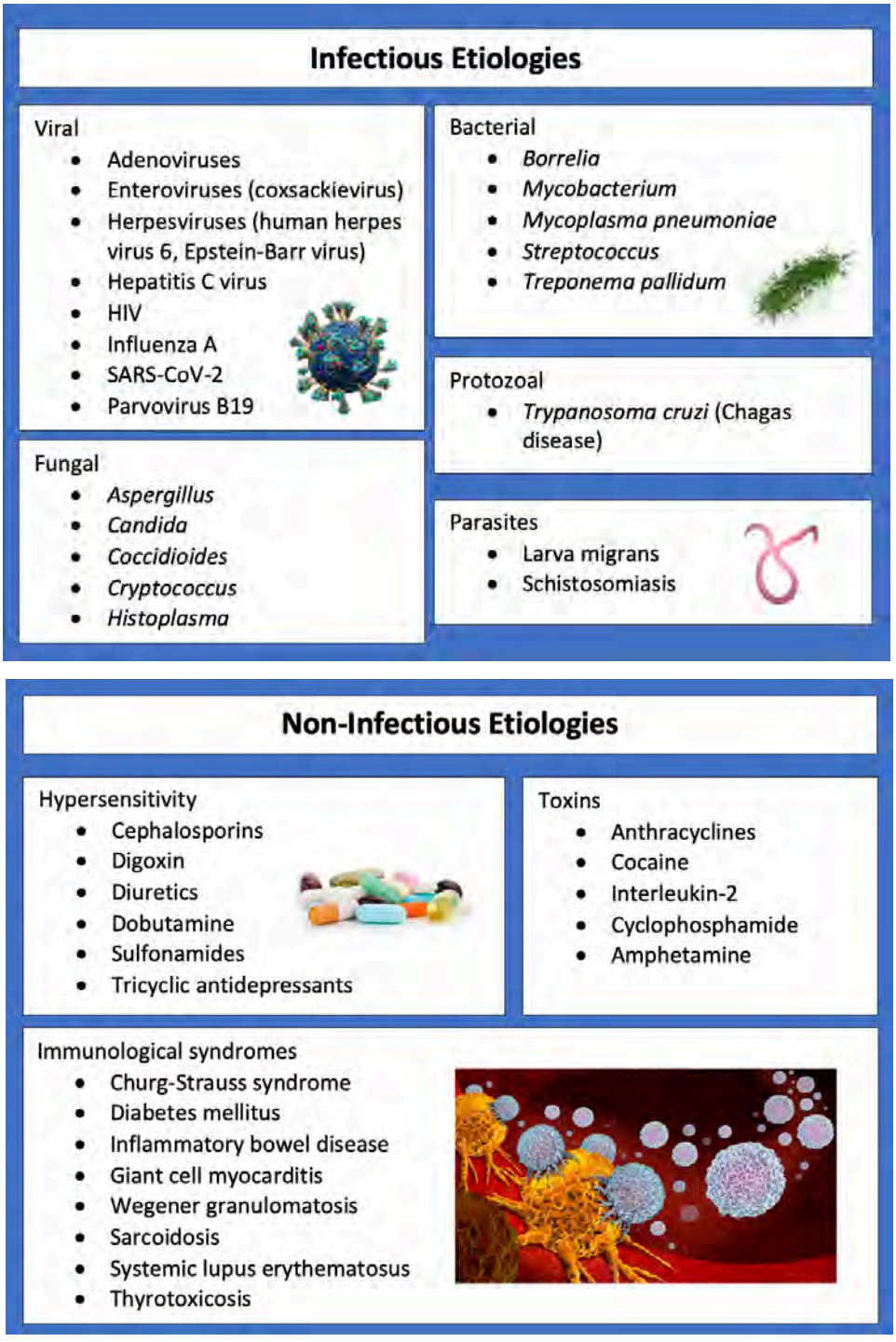
The most common viruses identified in myocarditis are coxsackie B3 virus, parvovirus B19, human herpes virus 6 (HHV6), human immunodeficiency virus (HIV), cytomegalovirus, Epstein-Barr

virus, and influenza.[3,4] In the Marburg Myocarditis Registry, a large cohort of patients with suspected myocarditis who underwent EMB, parvovirus B19 was the most common cause of myocarditis and comprised 28% of cases.[13] In contrast, HHV6 and coxsackie virus comprised less than 1% of cases.[13] The virus that causes COVID-19, SARS-CoV-2, is also suspected to be a cause of viral myocarditis, as outlined below. Experts have distinguished between virus-mediated myocarditis and virus-triggered myocarditis to differentiate between viruses that are known to be directly cytotoxic to the myocardium, such as coxsackie virus, and those that exert their effects via immune mechanisms in the absence of viral material in the myocardium, such as influenza.[5] The initial phase of attempted viral clearance by the innate immune system lasts approximately 7 days.[3] After the acute phase, patients may clear the virus and achieve full recovery, experience sustained viremia, or develop persistent inflammation after viral clearance that progresses to dilated cardiomyopathy.[3] The inflammatory phase is autoimmune in nature, with recruitment of natural killer cells and macrophages and the release of pro-inflammatory cytokines like IL-1/IL-2, interferon-gamma, and tumor necrosis factor.[4] Cardiomyopathy is characterized by myocyte destruction and hypertrophy leading to decreased ejection fraction via increased left-ventricular end-diastolic pressure.

COVID-19 Infection

The exact incidence of myocarditis related to COVID-19 is unknown, but it appears to be uncommon.[14,15] A retrospective study of hospitalized patients with COVID-19 estimated the risk of new heart failure diagnosis to be less than 1%.[15] In prospective studies of athletes with asymptomatic or mild COVID-19 who were screened with CMR, the incidence of myocarditis ranged between 0.3% and –3.0%.[5] One of the largest retrospective reviews included data from 56,963 hospitalized patients with COVID-19 from 23 hospitals in the United States and Europe. The authors identified 97 patients with possible myocarditis, of whom 54 had definite or probable myocarditis diagnosed by EMB or CMR.[14] This translated to an estimated prevalence of 2.4 cases of myocarditis per 1,000 hospitalizations. In this cohort, patients with myocarditis typically presented with chest pain and dyspnea, and almost 40% had a fulminant presentation requiring inotropes or circulatory support. More than half of identified patients with myocarditis did not have concurrent COVID-19 pneumonia.[14]

FIGURE 1. Infectious and Non-Infectious Etiologies of Viral Myocarditis



COVID-19 Vaccinations

There have also been cases of myocarditis reported in patients who had received one of the COVID-19 mRNA vaccines manufactured by Pfizer or Moderna.[16-20] It is important to note that myocarditis is not a unique complication to the COVID-19 vaccine, having been reported in association with vaccines against smallpox, influenza, and hepatitis B with an incidence of 0.1%

from 1990 to 2018.[21] Of the myocarditis events that were reported to the Vaccine Adverse Event Reporting System (VAERS) between December 2020 and August 2021, the majority of cases occurred after the second vaccine in young (median age 21) males with a median time to symptom onset of 2 days.[22] As of May 2022, verified VAERS reports indicated that the highest risk of myocarditis occurred in individuals 16-17 years of age, in which there were 298 verified reports after 12,687,076 doses (0.002%).[16] The American College of Cardiology notes that the clinical benefits of COVID-19 vaccination outweigh the risks of myocarditis, even among those at highest risk for myocarditis.[12] A recent conference abstract described the risk of post-vaccination myocarditis in children as being similar to the risk of being struck by lightning.[23] The majority of patients with reported myocarditis had a resolution of symptoms after initial hospitalization, with 87% of patients reported to VAERS experiencing a resolution of their presenting symptoms by hospital discharge.[22]

Treatment

There are no specific clinical practice guidelines for myocarditis treatment. Guidelines for the management of heart failure and arrhythmias should guide management where applicable, with treatments including beta blockers, renin-angiotensin system inhibitors, aldosterone antagonists, or diuretics. Expert consensus documents have been published by the American College of Cardiology specific to COVID-19-related myocarditis and by an international expert panel related to general myocarditis management.[5,12]

Patients with chronic autoimmune inflammatory cardiomyopathy who are known to be virus negative on EMB may benefit from immunosuppression with prednisone and azathioprine, but it is less clear whether the benefit extends to those with viral myocarditis.[8] Consensus statements recommend intravenous corticosteroids in the case of advanced or fulminant myocarditis with decompensated heart failure, or if high suspicion for autoimmune myocarditis exists.[5,12] Antiviral agents also do not have a clearly defined role in viral myocarditis. The betaferon in chronic viral cardiomyopathy (BICC) trial is one of the few studies to investigate a role of antiviral therapy—specifically, whether interferon beta-1b would benefit patients with heart failure from viral myocarditis. Patients, all of whom had confirmed adenovirus, enterovirus, or parvovirus B19, experienced enhanced viral clearance and improved quality of life and patient global assessment.[24] That said, antivirals are not specifically endorsed by either expert consensus document at this time due to the small body of evidence.[5,12]

The ACC Consensus Decision Pathways notes that fulminant myocarditis should be managed the same as cardiogenic shock from other etiologies, and that intravenous corticosteroids can be considered. Corticosteroids are also suggested in those with biopsy proven severe myocardial inflammatory infiltrates, with the caveat that these findings have rarely been reported with COVID-19. Patients with associated myopericarditis may be treated with low-dose colchicine or prednisone.[4,12] The recommendation to use nonsteroidal anti-inflammatory drugs (NSAIDs) remains a controversial issue. NSAIDS may be helpful to treat pain associated with pericarditis, but patients with left ventricular dysfunction are typically advised to avoid NSAIDS. In addition, athletes who are diagnosed with COVID-19-related myocarditis are advised to refrain from exercise for 3-6 months.[12]

Conclusion

Myocarditis is a rare complication of viral infections, including COVID-19, as well as mRNA-based COVID-19 vaccinations. Clinicians should have a high index of suspicion for myocarditis among patients with recent viral illness or COVID-19 vaccination who endorse symptoms of chest pain, dyspnea, and palpitations and who have nonspecific complaints including fever and fatigue. Diagnosing myocarditis in such patients requires laboratory evidence of myocardial damage and compatible findings on EKG, echocardiogram, CMR, and/or EMB. Treatment of myocarditis is largely supportive for dilated cardiomyopathy, but corticosteroids and other immunomodulatory agents could be considered in select populations. Clinicians should be advised that best practices in the management of viral myocarditis are still evolving.

Ami Leigh Schmidt and Etan Maistelman are 2023 Doctor of Pharmacy candidates at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI. Kristen Bunnell is an Assistant Professor of Clinical Sciences at the Medical College of Wisconsin School of Pharmacy and an infectious diseases pharmacist at Froedtert Hospital in Milwaukee, WI.

PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Disclosure: The authors declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

References

1. Dai H, Lotan D, Much AA, et al. Global, regional, and national burden of myocarditis and cardiomyopathy, 1990-2017. *Front Cardiovasc Med*. 2021;8:610989. doi:10.3389/fcvm.2021.610989
2. Putschoegl A, Auerbach S. Diagnosis, evaluation, and treatment of myocarditis in children. *Pediatr Clin North Am*. 2020;67(5):855-874. doi:10.1016/j.pcl.2020.06.013
3. Pollack A, Kontorovich AR, Fuster V, Dec GW. Viral myocarditis--diagnosis, treatment options, and current controversies. *Nat Rev Cardiol*. 2015;12(11):670-680. doi:10.1038/nrcardio.2015.108
4. Olejniczak M, Schwartz M, Webber E, Shaffer A, Perry TE. Viral myocarditis-incidence, diagnosis and management. *J Cardiothorac Vasc Anesth*. 2020;34(6):1591-1601. doi:10.1053/j.jvca.2019.12.052
5. Ammirati E, Frigerio M, Adler ED, et al. Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. *Circ Heart Fail*. 2020;13(11):e007405. doi:10.1161/CIRCHEARTFAILURE.120.007405
6. Ammirati E, Cipriani M, Moro C, et al. Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis: Multicenter Lombardy Registry. *Circulation.* 2018;138(11):1088-1099. doi:10.1161/CIRCULATIONAHA.118.035319
7. Younis A, Matetzky S, Mulla W, et al. Epidemiology characteristics and outcome of patients with clinically diagnosed acute myocarditis. *Am J Med.* 2020;133(4):492-499. doi:10.1016/j.amjmed.2019.10.015
8. Tschope C, Cooper LT, Torre-Amione G, Van Linthout S. Management of myocarditis-related cardiomyopathy in adults. *Circ Res*. 2019;124(11):1568-1583. doi:10.1161/CIRCRESAHA.118.313578
9. Bagnall RD, Weintraub RG, Ingles J, et al. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med*. 2016;374(25):2441-2452. doi:10.1056/NEJMoa1510687
10. Shatz A, Hiss J, Arensburg B. Myocarditis misdiagnosed as sudden infant death syndrome (SIDS). *Med Sci Law.* 1997;37(1):16-18.

doi:10.1177/002580249703700104
11. Luetkens JA, Faron A, Isaak A, et al. Comparison of original and 2018 Lake Louise criteria for diagnosis of acute myocarditis: results of a validation cohort. *Radiol Cardiothorac Imaging.* 2019;1(3):e190010. doi:10.1148/ryct.2019190010
12. Writing C, Gluckman TJ, Bhave NM, et al. 2022 ACC expert consensus decision pathway on cardiovascular eequelae of COVID-19 in Adults: myocarditis and other myocardial involvement, post-acute sequelae of SARS-CoV-2 infection, and return to play: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2022;79(17):1717-1756. doi:10.1016/j.jacc.2022.02.003
13. Maisch B, Alter P. Treatment options in myocarditis and inflammatory cardiomyopathy: focus on i.v. immunoglobulins. *Herz.* 2018;43(5):423-430. doi:10.1007/s00059-018-4719-x
14. Ammirati E, Lupi L, Palazzini M, et al. Prevalence, characteristics, and outcomes of COVID-19-associated acute myocarditis. *Circulation.* 2022;145(15):1123-1139. doi:10.1161/CIRCULATIONAHA.121.056817
15. Alvarez-Garcia J, Jaladanki S, Rivas-Lasarte M, et al. New heart failure diagnoses among patients hospitalized for COVID-19. *J Am Coll Cardiol.* 2021;77(17):2260-2262. doi:10.1016/j.jacc.2021.03.006
16. Selected adverse events reported after COVID-19 vaccination. Centers for Disease Control and Prevention. Updated 2022 May 16. Accessed May 24, 2022. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html
17. Abu Mouch S, Roguin A, Hellou E, et al. Myocarditis following COVID-19 mRNA vaccination. *Vaccine.* 2021;39(29):3790-3793. doi:10.1016/j.vaccine.2021.05.087
18. Anastassopoulou C, Hatziantoniou S, Vlachopoulos C, et al. Temporal relationship of myocarditis and pericarditis following COVID-19 vaccination: a pragmatic approach. *Int J Cardiol.* 2022;doi:10.1016/j.ijcard.2022.04.024
19. Bellos I, Karageorgiou V, Viskin D. Myocarditis following mRNA Covid-19 vaccination: a pooled analysis. *Vaccine.* 2022;40(12):1768-1774. doi:10.1016/j.vaccine.2022.02.017
20. Power JR, Keyt LK, Adler ED. Myocarditis following COVID-19 vaccination: incidence, mechanisms, and clinical considerations. *Expert Rev Cardiovasc Ther.* 2022:1-11. doi:10.1080/14779072.2022.2066522
21. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. *Circulation.* 2021;144(6):471-484. doi:10.1161/CIRCULATIONAHA.121.056135
22. Oster ME, Shay DK, Su JR, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. *JAMA.* 2022;327(4):331-340. doi:10.1001/jama.2021.24110
23. Aimo A CM, Emdin M, Clerico A. P402 COVID-19 vaccination in children aged 6-17 years carries a similar risk of fatal or life-threatening myocarditis than being struck by lightning. *European Heart Journal Supplements.* 2022;24(Suppl C)doi:suac012.388
24. Schultheiss HP, Piper C, Sowade O, et al. Betaferon in chronic viral cardiomyopathy (BICC) trial: effects of interferon-beta treatment in patients with chronic viral cardiomyopathy. *Clin Res Cardiol.* 2016;105(9):763-773. doi:10.1007/s00392-016-0986-9

Original Work

Adopting Health Literacy Best Practices Through Systems Change to Improve Medication Directions and Adherence

by Bhumi Khambholja, PharmD, MS, Stan Hudson, MA, Michele Erikson, George E. MacKinnon III, PhD, MS, Kenneth G. Schellhase, MD, MPH

Abstract

Gaps in communication and misinterpretation of medication directions can cause medication errors by patients and caregivers that can lead to poor adherence. Health systems should adopt universal health literacy precautions to improve how medication information is communicated for patient engagement. Wisconsin Health Literacy and its academic partners at the Medical College of Wisconsin are working to improve the use of clear and explicit directions by prescribers through systems change and adoption of Universal Medication Schedule directions. Currently, there has not been widespread implementation of Universal Medication Schedule directions, and a multi-disciplinary approach is required. Implementation of Universal Medication Schedule directions as a standard should be part of the model to address poor adherence and patient safety, and improve chronic disease management.

Health literacy can be defined two ways: 1) as the degree to which individuals have the ability to find, understand, and use information and services to inform health-related decisions and actions for themselves and others; and 2) as the degree to which organizations enable individuals to find, understand, and use information and services to make health-related decisions and actions for themselves and others.[1] Although there are certain characteristics that might put a person at higher risk for lower health literacy (such as being older in age, having limited education, having limited English proficiency, or being at a lower income level), it is important to recognize that health literacy is fluid and situational.[2,3] Any person can experience lower health literacy in a specific situation or when under stress or pain. Overall, gaps in health literacy have been associated with decreased secondary prevention, poor health status, and increased hospitalizations and emergency room visits.[3]

Many prescription medication directions require interpretation by patients, and misinterpretation can lead to undertreatment, overtreatment, or poor control of their health conditions. Research has shown that approximately 50% of prescription medication is not taken correctly, resulting in approximately 125,000 deaths, 10% of hospitalizations, and between $100 billion and $289 billion in costs annually.[4] Using patient-friendly language and precise instructions during patient education or medication reviews is an important strategy to improve patient understanding of medications. In addition, since patients are often inundated with health information, clear and explicit written medication directions are required. The prescription medication label is often the only source of information patients have in order to remember how to take their medication correctly and prevent medication-related issues. This is particularly important for chronic disease management and prevention of further complications.

Electronic prescribing greatly improved the readability of prescriptions for pharmacists; however, more focus is needed to improve the ability of patients to correctly understand and act upon medication directions on the label. The use of medical jargon or omission of key information are issues that community pharmacists often encounter and address. The issue also goes deeper than this, as the health literacy issues patients experience are often silent and unknown to healthcare professionals. The meaning of commonly used terms and frequencies in medication directions may not be known to all patients, resulting in medication not being taken at the right time, the right way, or at all. Verbally expressing understanding also does not always correlate to patients demonstrating how to take their medication correctly.[5] Since it is difficult to assess a person's health literacy at a specific point in time, it is important that there are universal precautions in place: practices and systems to make the clear communication of health information a standard. These systems improve patient engagement in their care.

Medication Label Initiative

Wisconsin Health Literacy (WHL), a division of Wisconsin Literacy, Inc. is a non-profit organization based in Madison, WI that works to improve health literacy across the state and beyond its borders. It accomplishes this by working with healthcare organizations to improve clear communication of health information and by developing community programs to address public health challenges. WHL has been working in conjunction with its academic partner at the Medical College of Wisconsin to improve the adoption of patient-centered prescription labels. The first three phases focused on community pharmacies and resulted in 1 in 5 pharmacies in Wisconsin implementing U.S. Pharmacopeia prescription label standards with improved readability based on patients' preferences and needs. In phase 4, WHL is working with academic, pharmacy, medical, health administrator,

and health information technology partners across the state to improve the use of clear directions by prescribers.

Universal Medication Schedule

Universal Medication Schedule (UMS) directions use health literacy best practices, such as using numerals instead of spelled-out numbers; sentence case; and explicit "morning," "noon," "evening," and "bedtime" timings. They provide clear and simple directions for patients to improve self-management, and they were created in response to the need to standardize prescription directions to prevent adverse drug events (Figure 1).[6]

Patients who have lower health literacy, take complex drug regimens, and experience poor communication from their providers are more likely to be non-adherent.[7,8] Addressing health literacy through systems change was recommended as a method to address medication adherence and management of heart failure by the American College of Cardiology.[9] Solutions to non-adherence are multi-pronged, require a team-based approach, and include providing actionable, patient-friendly medication directions.[8,9]

FIGURE 1. Example of Regular Prescription Directions and the Equivalent UMS Directions

Regular Directions	*UMS Directions*
Take one tablet by mouth twice daily	Take 1 tablet by mouth in the morning and 1 tablet in the evening
Take one tablet by mouth every 12 hours	
Take one tablet by mouth at 8a and 8p	

Patients are able to demonstrate how to take their medication better with UMS directions compared to directions with hourly intervals, times per day, or even specific times.[10] This is postulated to be due to the need for math with hourly frequencies, lack of specificity with per day frequencies, and specific times not working with patients' schedules.[10] Without intervention, patients are unlikely to consolidate the number of times per day they take medications, which contributes to poor adherence.[11] UMS directions have been associated with improved understanding of when to take medication by patients and improved adherence for patients who take medication more than one time a day or are over 65 years old.[10,12-15] Simplifying drug regimens and fitting them into a patient's schedule are important strategies to combatting non-adherence. Some pharmacy labels have already included a color-coded UMS pictogram to help patients take their medication at the right time of day (Figure 2). Discharge instructions often include a medication schedule for patients also (Figure 3). This type of visualization could help patients with limited English proficiency understand medication directions. Improving the use of UMS directions when prescribing reduces discrepancies between different sources of information, decreasing the risk of misunderstandings by patients. UMS directions are considered a best practice by the National Council for Prescription Drug Programs and are supported by the Structured and Codified Sig Format, which follow a defined format so that directions are appropriately transmitted electronically.[16] Currently, they have also been translated and shown to improve understanding of directions and consolidation of drug regimens in patients with limited English proficiency whose primary language was Spanish, Russian, Korean, Chinese, or Vietnamese.[13,17] Most daily medications for adults can fit the UMS format.[6] An expansion of UMS directions that uses a 'Take-Wait-Stop' approach to prescribing as-needed opioid pain medication is also being studied to assess the impact on safe opioid use.

Objective

Although the use of UMS directions has repeatedly been shown to be beneficial for patients, they have not yet been put into widespread practice. Barriers to implementation include lack of awareness of their benefits, not being incorporated into electronic prescribing systems, and costs to implement new processes. Pharmacists pay significant attention to the barriers patients face to taking their medication

FIGURE 2. Example of a UMS Pictogram for Prescription Label

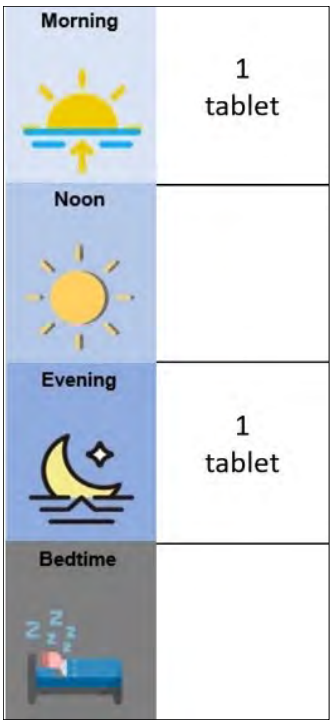


FIGURE 3. Example of a Medication Schedule Given to Patients at Discharge

Medicine Name and Strength	Morning	Noon	Evening	Bedtime
				
Metformin 500mg	1	1	1	
Glipizide ER 10mg	1			
Gabapentin 500mg	1		1	
Metoprolol 50mg	1		1	

correctly, and already provide a number of solutions to address poor adherence, such as motivational interviewing, medication therapy management sessions, medication synchronization, refill alerts, and compliance packaging. Yet there remains a need for prescribers to use clear and explicit medication directions. The goals of this project are to improve the use of UMS directions and change prescribing habits to become more patient centered.

Adoption of Explicit Directions by Prescribers

A pilot study to implement UMS directions was conducted at an outpatient clinic. The process of electronically prescribing medication was kept the same and physician champions improved awareness of the need for this change. Without the need for added steps or further cognitive burden, and by understanding the benefits to their patients, prescribers started utilizing UMS directions.

WHL will continue working with health systems across the state to make the use of UMS directions as easy as possible for prescribers. To assure that any changes to electronic prescribing meets the needs of the end user, one electronic health record software vendor has created a UMS sig feature, where traditional directions are automatically converted to the UMS format prior to being electronically signed and submitted to an outpatient pharmacy. Implementation of this feature is one piece of shifting prescribing habits to becoming more intentional and changing how medication directions are communicated for better patient engagement.

It will also be important for prescribers to adopt other electronic prescribing best practices, such as using discrete directions where possible; avoiding splitting directions between the 'sig' and 'notes' fields; and reviewing every prescription before transmission. Leadership support across the healthcare ecosystem and advocacy will be necessary for adoption of clearer medication directions for patients. Listening to the voice of the patient is also key to patient-centered care, and their needs and concerns will be used as a driver for change in this initiative. Both a widespread awareness campaign and champions to advocate for change will be utilized. WHL is also working on integrating the concept of UMS and utilizing clear directions for patients into pharmacy and medical student education and training.

Systems Change

The movement of new knowledge from research studies to real-world practices requires a multidisciplinary approach. Health administrators, prescribers, pharmacists, and health information technology professionals are important stakeholders in adopting clear and explicit medication directions. The use of champions has been shown to be vital for innovation and change, as they are able to effectively build and communicate a vision for change; navigate the power dynamics and social environment within a health system; address and understand concerns; and naturally advocate for change among peers to build confidence.[18] Patient-centered care principles are now often integrated into the training of health professionals, leading to the generation of champions for change on a larger scale.

Rogers' Diffusion of Innovation Theory was used in the previous three

Commentary by Dr. Schellhase and Dr. Mackinnon

Addressing the overlap of health literacy and medication adherence is a priority whose time has come. Cardiovascular disease is only one of many domains where the importance of adherence has come into stark relief. Recent clinical guidance from the American College of Cardiology regarding the management of congestive heart failure (CHF)—one of the most common and costly conditions in the U.S.—cites medication adherence as a "top 10" pivotal issue in heart failure treatment.[9] This is due to the profound influence of medication use and subsequent adherence on the effectiveness of medical therapy for CHF,[9] yet estimates of medication non-adherence range from 20% to 50%. Similarly, the U.S. Surgeon General's 2020 Call to Action to Control Hypertension highlighted the importance of adherence.[21] In a conceptual model that diagrams the influences on disparities in hypertension control, medication adherence is a key patient-level factor that influences hypertension control.[21] The report goes on to invoke the need for a specific strategy for medication adherence as part of protocols for hypertension management.[21]

However, neither of these authoritative publications has explicitly drawn out the connection between health literacy and adherence. While health literacy may be a patient-level factor, addressing gaps in health literacy cannot be solved primarily at the individual patient level. We need to meet patients where they are with the literacy level they have, now. Consequently, it takes a systems approach, such as the one described in this article, to make prescription bottle labels more readable and understandable to patients with limited health literacy. We need to embrace new and emerging technologies and leverage existing platforms (e.g., electronic health records and prescribing) to address such disparities in health literacy which directly impact medication adherence and tangential health outcomes. This work should be understood in a broader context of systematic ways to improve health outcomes, and reduce disparities in those outcomes, that do not rely on new advances in medical care. Through a coordinated and inclusive multidisciplinary approach, health systems, providers and pharmacies must work in tandem to address health disparities inclusive of health literacy that lead to suboptimal patient outcomes. It relies on us working to better deliver the outcomes that can and should be attained by current science—simply by helping patients take their medications as intended.

phases of the Medication Label Initiative to guide adoption of patient-centered labels in pharmacies, and it continues to explain how widespread implementation of UMS directions can occur.[19] Every organization will adopt change at a different rate based on its ability to tolerate a degree of uncertainty associated with change. Implementation of the UMS sig feature by early adopters will provide insights on successful implementation and daily functioning, trigger interest and discussion, and help motivate change at other organizations. Early adopters serve as a catalyst for more widespread adoption and commonly include health systems who have strong thought leaders, access to resources, and an established practice of inter-professional collaboration.[20] Health system-specific processes, culture, and social norms will influence the successful adoption of the UMS feature. For this particular initiative, health systems with the organizational structure to address health literacy issues within their organization will be able to better advocate for change and communicate why it is needed.

The role of community pharmacies and staff also cannot be overlooked. Certain characteristics of UMS, such as sentence case, using numerals instead of spelled out numbers, and a pictogram, can only be adopted at the pharmacy level. In the first phase of the Medication Label Initiative, pharmacists demonstrated a willingness and keen interest in making prescription labels easier to understand, and community pharmacies in Wisconsin were able to make some changes to standardize and format directions for clarity during Phases 2 and 3.[19] UMS also has the potential to aid the other adherence interventions pharmacists employ, such as motivational interviewing and medication organization during comprehensive medication reviews or adherence packaging. Overall, community pharmacy staff continue to play a key role in clear directions for patients.

Conclusion

Universal Medication Schedule directions improve understanding of when to take medication, simplify drug regimens, and can improve adherence. Implementation requires multiple members of the healthcare team and for all stakeholders to understand the needs of patients to effectively manage their medication regimens. Using unambiguous medication directions for patients to act upon is a move towards patient-centered care to engage patients in their care and improve chronic disease management.

Bhumi Khambholja is the Project Manager, Stan Hudson is the Health Literacy Director, and Michele Erikson is the Executive Director for Wisconsin Health Literacy, a division of Wisconsin Literacy, in Madison, WI. George E. Mackinnon is the Dean of the School of Pharmacy at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI. Kenneth G. Schellhase is a Professor in the Department of Family and Community Medicine at the Medical College of Wisconsin in Milwaukee, WI.

Acknowledgements : Funding is provided by the Advancing a Healthier Wisconsin Endowment of the Medical College of Wisconsin. A special thank you to the members of the Project Advisory Council who provide invaluable support and expertise.

Disclosures: George Mackinnon is on the Pharmacy Society of Wisconsin's Board of Directors. The authors declare no other real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

IRB: The Institutional Review Board at the Medical College of Wisconsin determined that Phase 4 of the Medication Label Initiative does not constitute as human subjects research on July 30, 2021.

References

1. Office of Disease Prevention and Health Promotion. Health Literacy in Healthy People 2030. Health.gov. 2021. Accessed February 17, 2022. https://health.gov/our-work/national-health-initiatives/healthy-people/healthy-people-2030/health-literacy-healthy-people-2030
2. Agency for Healthcare Research and Quality. AHRQ Health Literacy Universal Precautions Toolkit. 2nd Edition. AHRQ.gov. 2020. Accessed February 10, 2022. www.ahrq.gov/health-literacy/improve/precautions/index.html
3. Office of Disease Prevention and Health Promotion (2020). Health Literacy. Healthypeople.gov. 2018. Accessed February 11, 2022. https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-health/interventions-resources/health-literacy
4. Viswanathan M, Golin CE, Jones CD, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Ann Intern Med*. 2012;157(11):785-795. doi: 10.7326/0003-4819-157-11-201212040-00538
5. Davis TC, Wolf MS, Bass PF, et al. Literacy and misunderstanding prescription drug labels. *Ann Intern Med.* 2006;145(12):887. doi:10.7326/0003-4819-145-12-200612190-00144
6. Institute of Medicine 2008. Standardizing medication labels: confusing patients less: workshop summary. Washington, DC: The National Academies Press. doi: 10.17226/12077
7. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353(5):487-497. doi:10.1056/nejmra050100
8. Bosworth HB, Granger BB, Mendys P, et al. Medication adherence: a call for action. *Am Heart J.* 2011;162(3):412-424. doi:10.1016/j.ahj.2011.06.007
9. Maddox TM, Januzzi JL, Allen LA, et al. 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction. *J Am Coll Cardiol.* 2021;77(6):772-810. doi:10.1016/j.jacc.2020.11.022
10. Davis TC, Federman AD, Bass PF, et al. Improving patient understanding of prescription drug label instructions. *J Gen Intern Med.* 2008;24(1):57-62. doi:10.1007/s11606-008-0833-4
11. Wolf MS, Curtis LM, Waite K, et al. Helping patients simplify and safely use complex prescription regimens. *Arch Intern Med*. 2011;171(4). doi:10.1001/archinternmed.2011.39
12. Wolf MS, Davis TC, Curtis LM, et al. Effect of standardized, patient-centered label instructions to improve comprehension of prescription drug use. *Med Care.* 2011;49(1):96-100. doi:10.1097/mlr.0b013e3181f38174
13. Bailey SC, Sarkar U, Chen AH, Schillinger D, Wolf MS. Evaluation of language concordant, patient-centered drug label instructions. *J Gen Intern Med*. 2012;27(12):1707-1713. doi:10.1007/s11606-012-2035-3
14. Wolf MS, Davis TC, Curtis LM, et al. A patient-centered prescription drug label to promote appropriate medication use and adherence. *J Gen Intern Med.* 2016;31(12):1482-1489. doi:10.1007/s11606-016-3816-x
15. Wolf MS, Taitel MS, Jiang JZ, et al. Prevalence of universal medication schedule prescribing and links to adherence. *Am J Health Syst Pharm*. 2020;77(3):196-205. doi:10.1093/ajhp/zxz305
16. National Council for Prescription Drug Programs. SCRIPT implementation recommendations. NCPDP.org. 2021. Accessed January 20, 2022. https://www.ncpdp.org/NCPDP/media/pdf/SCRIPT-Implementation-Recommendations.pdf
17. Agency for Healthcare Research and Quality. Explicit and standardized prescription medicine instructions. AHRQ.gov. 2020. Accessed February 10, 2022. www.ahrq.gov/health-literacy/improve/pharmacy/instructions.html
18. Shaw EK, Howard J, West DR, et al. The role of the champion in primary care change efforts: From the State Networks of Colorado Ambulatory Practices and Partners (Snocap). *J Am Board Fam Med*. 2012;25(5):676-685. doi:10.3122/jabfm.2012.05.110281
19. Sparks SW, Schellhase KG, Werner LB, et al. Adopting patient-centered prescription medication labels in Wisconsin. *J Pharm Soc Wis*. 2018;21(4):30-36. Accessed February 10, 2022. https://www.jpswi.org/jpswja18.html
20. Dearing JW, Cox JG. Diffusion of innovations theory, principles, and practice. *Health Aff (Milwood).* 2018;37(2):183-190. doi:10.1377/hlthaff.2017.1104
21. U.S Department of Health and Human Services. The Surgeon General's call to action to control hypertension. CDC.gov. 2020. Accessed March 25, 2022. https://www.cdc.gov/bloodpressure/docs/SG-CTA-HTN-Control-Report-508.pdf

Original Work

Baricitinib (Olumiant®) Thromboembolic Event in Patient Receiving Full-dose Anticoagulation

by Alexis A. Vandehey PharmD, Megan A. Avery 2022 PharmD Candidate, Jennifer A. Esch PharmD BCPS, Jessica S. Thompson APNP

Abstract

We describe the case of a 69-year-old male on baricitinib for COVID-19 treatment who developed bilateral deep vein thromboses while on full-dose anticoagulation with apixaban. Patients should be closely monitored for signs of venous thromboembolism while on baricitinib, even while on anticoagulation.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), better known as the coronavirus disease 2019 (COVID-19), is an infectious disease impacting public health globally. As the disease continues to spread, treatment options are emerging. Baricitinib has demonstrated improved time to recovery in patients with COVID-19, along with standard of care.[1] Baricitinib is a selective and reversible Janus kinase (JAK) 1 and 2 inhibitor. It has known anti-inflammatory effects in patients with autoimmune diseases, such as rheumatoid arthritis.[2] Its anti-cytokine properties and ability to target host proteins give it potential for the treatment of COVID-19.[3]

Baricitinib has a black box warning for thromboembolic risk; that is, deep vein thrombosis (DVT) and pulmonary embolism (PE)]. It also has a warning for cardiovascular risk (stroke).[1] There have been higher incidences of venous thromboembolic events (VTE) reported in patients on baricitinib versus placebo, even in those on prophylactic anticoagulation. However, there have not been any reports of thromboembolic events noted with baricitinib use while on therapeutic anticoagulation dosing. Due to these reactions, it is not considered a first line agent for the treatment of COVID-19. It is reserved for patients with progressive oxygen requirements despite standard of care.[3]

A literature search was conducted in MedLine and PubMed using the following search terms: (baricitinib and thrombosis) and (baricitinib and thromboembolism). No results returned involving reports of baricitinib use during COVID-19 treatment and occurrence of VTE, while also on therapeutic anticoagulation. The following case is a report of a patient who developed bilateral DVTs while on baricitinib, along with therapeutic anticoagulation. The Research Subject Protection Program at our health institution determined that this report does not constitute as human subject research and does not require Institutional Review Board oversight.

Case Presentation

In August 2021, a 69-year-old white male was admitted to the hospital with a chief complaint of worsening shortness of breath. He first tested positive for COVID-19 11 days prior to admission. He received casirivimab and imdevimab three days prior to admission, completed 10 days of dexamethasone, and was on oxygen at home for the treatment of COVID-19. He received two doses of the Pfizer-Biotech COVID-19 vaccine series in March of 2021 (booster doses were not approved at that time). Upon admission, a chest CT was completed, and no PE was detected. An ultrasound was not completed at this time as there were no signs of DVT.

Pertinent past medical history included

TABLE 1. Patient Lab Values During Admission

Lab Value	*Reference Range*	*ED Admission*	*Week 1* *Prior to start of baricitinib*	*Week 2* *Day ultrasound showed bilateral deep vein thrombosis*	*Week 3* *After discontinuation of baricitinib*
Creatinine	0.67-1.17 mg/dL	0.87	0.71	0.56	0.54
Creatinine clearance	97-137 mL/min	108	>120	>120	>120
Aspartate transaminase	≤37 Units/L	19	34	59	26
Alanine aminotransferase	<64 Units/L	22	54	199	118
Alkaline phosphatase	45 – 117 Units/L	88	76	106	84
Total bilirubin	0.2 - 1.0 mg/dL	0.4	0.4	1.4	1.4
Platelets	150 – 450 K/mcL	392	373	252	126
Hemoglobin	13.0 - 17.0 g/dL	12.8	11.7	12.4	9.3
Hematocrit	39-51%	38.1	34.9	36.3	27.3

interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), and atrial fibrillation. He had no relevant allergies. The patient was a former smoker (40 pack year history), and reported rare alcohol use and no illicit drug use. At the time of admission, his weight was 96 kilograms and he was 1.88 meters tall. Current home medications included alendronate 35 mg weekly, cetirizine 10 mg daily, cholecalciferol 2000 units daily, doxazosin 4 mg daily, fish oil 1000 mg twice daily, montelukast 10 mg daily, multivitamin daily, pantoprazole 40 mg daily, metoprolol tartrate 25 mg twice daily, apixaban 5 mg twice daily, mycophenolate 1500 mg twice daily, and psyllium 2.6 g daily. The patient was adherent to his medications and reported no missed doses. Significant labs are seen in Table 1. Labs were notable for an elevated serum creatinine upon admission and mild transaminitis while taking baricitinib and remdesivir.

At the time of admission, the patient was started on remdesivir 200 mg once followed by 100 mg daily for 5 days and baricitinib 4 mg daily for 14 days for COVID-19 treatment, due to his worsening respiratory status. Valacyclovir 500 mg twice daily for 28 days was also started for herpes simplex virus (HSV) prophylaxis. The patient was already taking apixaban 5 mg twice daily for stroke prevention following his atrial fibrillation diagnosis in July of 2021. The apixaban was continued inpatient for stroke prevention and venous thromboembolism prophylaxis. Ten days into treatment with baricitinib, it was noted that the patient had swelling in both legs and an ultrasound confirmed that the patient had developed bilateral lower extremity DVTs. Given this finding, baricitinib was discontinued, as well as apixaban due to possible treatment failure. The patient was instead started on enoxaparin 100 mg subcutaneously twice daily for DVT treatment, with the addition of warfarin. Enoxaparin was able to be discontinued after INR was therapeutic (2.0–3.0) for 48 hours. He was admitted for a total of 26 days.

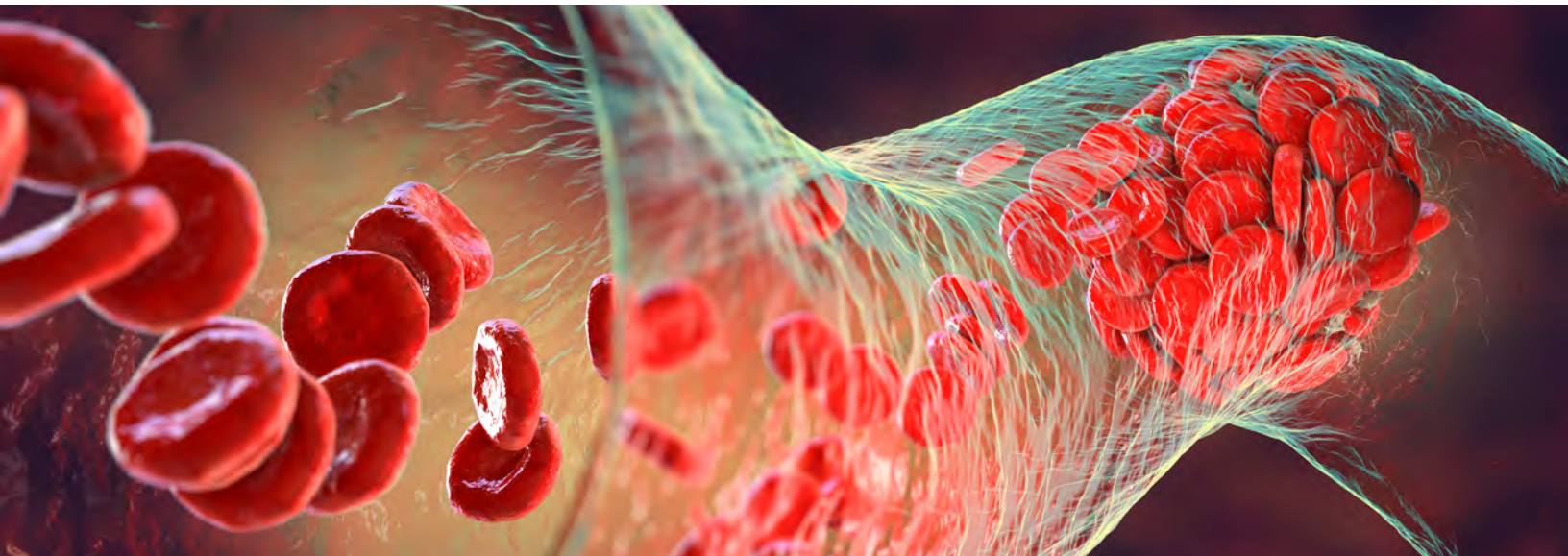
Discussion

Multiple scenarios were evaluated for our patient when searching for a cause of his bilateral DVTs. VTE is a well-known side effect of baricitinib. VTE has been appearing in patients with COVID-19 as well.[1,4] Studies have also reported coagulation abnormalities in patients with COVID-19. A systematic review found a 14% incidence of VTE across all patients with COVID-19, with VTE occurring in almost 23% of patients in the intensive care unit (ICU).[4] Current guidelines from the National Institutes of Health recommend thromboprophylaxis anticoagulation dosing in patients with severe COVID-19, in the absence of high bleed risk.[5]

Baricitinib was originally approved in 2018 for rheumatoid arthritis.[6] In November 2020, the FDA granted Emergency Use Authorization (EUA) of baricitinib for use in COVID-19 patients for 14 days, or until hospital discharge.[7] It is thought that baricitinib inhibits the intracellular signaling pathway of cytokines, which are often elevated in patients with severe COVID-19. Two phase 3, randomized, double-blind controlled clinical trials evaluated baricitinib use in patients with COVID-19.[2,8] Despite COVID-19 and baricitinib both being risk factors for increased VTE, treatment with baricitinib did not show an increased risk compared to placebo.

There are a few aspects that may have led to treatment failure in this particular patients; however, most of those were able to be ruled out. While it is recommended to decrease the dose of baricitinib to 2mg daily for patients with estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73m2, this patient's eGFR was >90 mL/minute/1.73 m2; thus, baricitinib was dosed appropriately.[1] Additionally, VTE prophylaxis is required with the administration of baricitinib; however, this patient was on full-dose anticoagulation with apixaban when he developed bilateral DVTs. There is limited data regarding the dosing of apixaban in obese patients (> 120kg), as previous studies have noted a decrease in maximum concentration (Cmax) and area under the curve (AUC) in this patient population. Yet there are still no specific dosing adjustments recommended.[9] Importantly, the patient in this case had an actual body weight of 96 kg; therefore, this was not likely a reason of his treatment failure.

Other potential causes of treatment failure could have been due to medication interactions. There was a notable interaction between apixaban and diltiazem, with the potential to increase apixaban concentration. We would expect this to increase the risk of bleeding, not clotting as experienced by this patient, making baricitinib the likely culprit. There was also a drug-drug interaction between baricitinib and the patient's home medication of mycophenolate, with the potential to enhance immunosuppression. However, this did not play a role, because mycophenolate, used in this patient for interstitial lung



disease, was not continued during the hospital stay.

Conclusion

This patient case demonstrates that the overlapping pharmacodynamic risk factors for VTE, including hospitalization, active COVID-19 infection, and concomitant use of baricitinib therapy, resulted in breakthrough thrombosis despite full dose anticoagulation with apixaban for underlying atrial fibrillation. Providers should be aware of this adverse reaction and monitor early and often, even if a patient is on full anticoagulation. Additional reports of VTE occurrence on full dose anticoagulation may be expected, as baricitinib is used for COVID-19 therapy in more patients as the pandemic continues. Further studies to define the optimal anticoagulation regimen for patients requiring baricitinib for COVID-19 infection are still needed.

Alexis Vandehey is a PGY-1 Pharmacy Resident at Aurora BayCare Medical Center in Green Bay, WI. Megan Avery is a 2022 Doctor of Pharmacy Candidate at the University of Wisconsin-Madison School of Pharmacy in Madison, WI. Jennifer Esch is a Clinical Pharmacist at Aurora BayCare Medical Center in Green Bay, WI. Jessica Thompson is an Advanced Practice Nurse Practitioner at Aurora BayCare Medical Center in Green Bay, WI.

PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Disclosures: The authors declare no other real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Corresponding Author:
alexis.vandehey@aah.org

References

1. Olumiant® (baricitinib) [prescribing information]. Indianapolis, IN: Lilly USA LLC; December 2021.
2. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalized adults with COVID-19 (COV-BARRIER): a randomized, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med.* 2021;9(10):e102. doi:10.1016/S2213-2600(21)00331-3
3. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet.* 2020;395(10223):e30-e31. doi: 10.1016/S0140-6736(20)30304-4
4. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Res Pract Thromb Haemost.* 2020;4(7):1178-1191. doi:10.1002/rth2.12439
5. COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Updated May 31, 2022. https://www.covid19treatmentguidelines.nih.gov
6. Genovese MC, Kremer J, Zamani O, et al. Barcitinib in patients with refractory rheumatoid arthritis. *N Engl J Med.* 2016;374(13):1243-1252. doi: 10.1056/NEJMoa1507247
7. Olumiant® (baricitinib) [Emergency Use Authorization]. Indianapolis, IN: Lilly USA LLC; December 2021
8. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med.* 2021;384(9):795-807. doi:10.1056/NEJMoa2031994
9. Upreti VV, Wang J, Barrett YC, et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. *Br J Clin Pharmacol.* 2013;76(6):908-916. doi:10.1111/bcp.12114

MEDICAL COLLEGE OF WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Molnupiravir: Review of a New Oral Antiviral Agent Approved for Emergency Use Authorization in the United States for Coronavirus Disease 2019

by Vanessa Lei, PharmD Candidate 2023, Payeng Lor, PharmD Candidate 2023, Vanessa Sanchez, PharmD Candidate 2023, Kong Choua Thao, PharmD Candidate 2023, Zachary Hovis, PharmD, BCACP

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory illness caused by the novel coronavirus SARS-CoV-2 and resulting in an ongoing global pandemic. As of January 2022, SARS CoV-2 totaled 64,720,612 cases and 843,718 deaths in the U.S. alone.[1] While all populations are at risk of contracting COVID-19, people who are older, are immunocompromised, or who have certain comorbidities (e.g. cardiovascular disease, diabetes, or chronic lung disease) have a much higher risk of progressing to severe disease and hospitalization.[2] Due to the high transmissibility and infectious nature of COVID-19, many preventive measures, such as the use of masks in public settings and social distancing, have been put into place nationally. These preventive measures play an essential role in combating widespread transmission of the novel coronavirus. Additionally, the development of numerous mRNA vaccines against COVID-19 have resulted in reduced transmission and hospitalization. Phase three trial data for one of the mRNA vaccines demonstrated an effectiveness rate of 94.1% for preventing laboratory-confirmed COVID-19 following full vaccination and 90% effectiveness rate six months post vaccination.[3-4] As of this writing on January 22, 2022, 80.2% of the U.S. population has received at least one dose of a COVID-19 vaccine.[5] While rates of vaccination are high, many individuals remain hesitant to get vaccinated due to various psychosocial reasons, with the most prevalent being concerns about vaccine side effects, and mistrust of COVID-19 vaccines in terms of safety or efficacy.[6] Those who are unvaccinated continue to experience high rates of hospitalizations and deaths, with unvaccinated individuals being 16 times more likely to become hospitalized and 15 times more likely to die from COVID-19 compared to fully vaccinated individuals.[7]

While highly effective, vaccines alone are inadequate for reducing the full disease burden of COVID-19 in the United States, given the limitations of vaccine uptake.[3,8] This created a need for a therapy that could reduce the risk of disease progression in patients with mild to moderate COVID-19. This led to the emergence of several new oral antiviral agents such as molnupiravir, nirmatrelvir, and ritonavir for treatment. Molnupiravir was the first oral antiviral agent to receive authorization to treat COVID-19 in the world, approved on November 4, 2021, by the United Kingdom Medicine and Healthcare Product Regulatory Agency.[9] This was followed by the U.S. Food and Drug Administration (FDA) issuing an emergency use authorization (EUA) on December 23, 2021, for the use of molnupiravir in COVID-positive patients with high risk of progressing to severe COVID-19.[10] This paper aims to evaluate the safety and efficacy of molnupiravir for treatment of mild to moderate COVID-19 based on current research and literature.

Market Analysis

As of this writing, remdesivir is currently the only FDA-approved medication for the treatment of COVID-19 infections in both hospitalized and outpatient patients.[11-12] It is administered intravenously and has demonstrated superiority in reducing recovery time for hospitalized patients with severe cases when compared to placebo.[13-14] Additionally, remdesivir demonstrated an 87% reduction in risk of hospitalization and death in non-hospitalized patients who were at an increased risk for worsening progression of COVID-19 with a three-day treatment course.[16] Given remdesivir's route of administration, a need still exists for a less invasive outpatient antiviral treatment option that would reduce the risk of disease progression in patients with mild to moderate infections.[3,15] Initially, hydroxychloroquine was thought to be beneficial for the treatment of COVID-19 and was given EUA by the FDA in March 2020, but that EUA was rescinded in June 2020 due to non-significant data after more extensive review.[17] In an observational study that evaluated the benefit of hydroxychloroquine for hospitalized patients, no significant difference in the end composite of intubation or death was observed among the two groups.[18] In another study focusing on the treatment for mild to moderate COVID-19 cases, hydroxychloroquine failed to show significant benefits and had an increase in cardiac adverse effects compared to the non-recipient group.[19] The ORCHID trial, designed to evaluate the efficacy and safety of hydroxychloroquine for COVID-19 patients, was discontinued as there was no clear benefit.[17]

As evidenced by the increasing number of patients hospitalized, partly due to the contagious Omicron COVID-19 variant, novel oral antiviral therapies are an

important avenue to explore to reduce the burden on health care systems. There are a few promising oral therapies with positive early results in current literature, including molnupiravir, nirmatrelvir, and ritonavir.[9] In the rest of this article, we will further explore molnupiravir.

Mechanism of Action

Molnupiravir works by introducing errors into the SARS-CoV-2 virus's genetic code, which prevents viral replication. Specifically, molnupiravir is a synthetic ribonucleoside derivative N-hydroxycytidine (NHC) prodrug that circulates systemically and is phosphorylated intracellularly to NHC triphosphate. NHC triphosphate is integrated into the viral RNA which misdirects the viral polymerase to incorporate either guanosine or adenosine leading to deleterious errors.[3,22] The accumulation of deleterious errors leads to a viral error catastrophe preventing replication.[23] Lee et al created a visual representation of the mechanism of action of molnupiravir.[24]

Pharmacokinetics

The pharmacokinetics of molnupiravir have been studied in healthy subjects in both single and multiple doses in fed and fasting states. Subjects include humans, mice, rats, dogs, monkeys, and ferrets.[25] A summary of the pharmacokinetics can be seen in Table 1.

Absorption:

Molnupiravir is a 5' -isobutyrate ester prodrug cleaved by esterase in the intestine and liver to be converted into NHC.[25] The absorption and conversion process of molnupiravir occurs very rapidly and maximum serum concentration is reached at around 1.5 hours. Administration of molnupiravir with food will decrease maximum serum concentration by 35% with no effect on area under the curve (AUC). Molnupiravir is reported to be well tolerated with minimal adverse effects.[22,24]

Distribution:

The mean volume of distribution of Molnupiravir was 142 liters when taking 800 mg every 12 hours.[22] In most species, tissues with the highest exposures include the lung and spleen, and the tissue with the lowest levels was the brain. The plasma protein binding of molnupiravir was not assessed since the molecule is not stable in plasma.[22,25]

Metabolism:

In vivo metabolism studies of molnupiravir were performed on Wistar Han rats and male intact beagle dogs.[22] After oral administration, there was a low recovery of molnupiravir and its metabolites in excreted waste, indicating how well molnupiravir was absorbed. It was confirmed in an in vitro study that the majority of the molnupiravir was metabolized to pyrimidine metabolites, with the major metabolite being uridine and the minor metabolites being cytidine monophosphate and uridine monophosphate. These metabolites were integrated into the endogenous pyrimidine pool, hence the low recovery in excreted waste.

Elimination:

Molnupiravir is excreted in urine as NHC and endogenous pyrimidine nucleosides, uridine or cytidine. Molnupiravir is calculated to have a half-life of about 3 hours, with the majority of the drug being excreted within the first 4 hours. There is no dose adjustment needed in patients with any degree of renal or hepatic impairment as there was no meaningful impact on the pharmacokinetics of NHC. It is important to note that studies have not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis, severe renal impairment, and end-stage renal disease (ESRD).[22,25]

Pharmacodynamics

A humanized mouse model (immunodeficient mice who were implanted with human lung tissue) was performed using infected lung only mice.[24] The model demonstrated a significant reduction of in vivo replication of SARS-CoV-2 in mice with infected lungs when molnupiravir was given prophylactically at a dose of 500 mg/kg.[24,25] Therapeutic administration also demonstrated reduction in SARS-CoV-2 but was largely dependent on time of treatment initiation.[27] Additionally, treatment with molnupiravir in infected ferrets displayed a significant reduction in SARS-CoV-2 viral load within 12 hours of initiating treatment, and furthermore, blocked transmission of SARS-CoV-2 to untreated ferrets after 30 hours of initiating treatment.[22, 25- 27]

Clinical Data

The phase three randomized controlled trial MOVe-OUT evaluated the safety and efficacy of molnupiravir in non-hospitalized patients infected with mild-moderate COVID-19 compared to placebo.[3] MOVe-OUT included 1,433 participants who were enrolled at 107 sites from 20 different countries and underwent randomization in a 1:1 ratio for either molnupiravir treatment or placebo treatment. Participants were to take 800 mg of molnupiravir orally twice daily for a period of five days, or placebo, and were followed through day 29. Inclusion criteria were current SARS-CoV-2 infection that had been laboratory confirmed with mild-moderate signs and symptoms occurring no more than five days prior. Additionally, eligible participants had to have at least one additional risk factor for the development of a serious COVID-19 infection such as age greater than 60 years old, active cancer, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), obesity (BMI ≥ 30 kg/m^2), serious heart conditions (heart failure,

TABLE 1. Pharmacokinetic of Molnupiravir after multiple oral administration of 800 mg every 12-hr[22]

Absorption	
T_{max} (hr)	1.50 [1.00 - 2.02]
Effect of food	35% reduction in C_{max}, no effect on AUC
Distribution	
Plasma Protein Binding	0%
Volume of Distribution (L)	142
Elimination	
T1/2 (hr)	3.3
Clearance (L/hr)	76.9
Fraction of dose excreted in urine over the time interval of 0-12 hr	3% as NHC, 81.6% as endogenous pyrimidine nucleoside

AUC = Area under the curve, NHC = N-hydroxycytidine

CAD, cardiomyopathies), or diabetes mellitus. Key exclusion criteria included anticipated hospitalization within the next 48 hours, dialysis, an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2, pregnancy, unwillingness to use contraception during the intervention period, severe neutropenia, low platelet count less than 100,000 per mcL, and vaccination against SARS-CoV-2. Baseline characteristics for both groups were statistically similar.

The primary efficacy endpoint for the trial was the incidence of hospitalization for any cause, or death, through day 29.[3] The primary safety endpoint was the incidence of adverse events with patients being evaluated for any drops in platelet count (less than 50,000 per mcL) and potential hepatotoxicity induced by the medication. Given data from the planned interim analysis at 50% enrollment, the MOVe-OUT trial was recommended to end recruitment early given positive efficacy results by an independent data monitoring committee. After the 29-day period, the primary efficacy endpoint was significantly lower in the molnupiravir group (7.3%) compared to the placebo group (14.1%) (P = 0.001). The percentage of participants with at least one adverse event was similar in both groups (30.4% in the molnupiravir group vs. 33.0% in the placebo). Deaths were reported less frequently in the molnupiravir group (2 deaths) compared to the placebo group (12 deaths) (95% CI: -2.7 to -5). Results were consistent in all subgroups based on gender, race, baseline COVID severity, and the specified risk factor (i.e. DM, age, CVD).

Conclusion

Molnupiravir is the first oral antiviral medication that has data supporting its safety and efficacy in treating mild to moderate SARS-CoV-2 infection. The importance of having an outpatient oral antiviral therapeutic option for high-risk individuals represents an important treatment breakthrough in the global fight to reduce the burden of COVID-19. Further studies should be done to evaluate the potential benefits of molnupiravir for the treatment of COVID-19 infections among vaccinated individuals, and as well as repeat infections, to help better inform clinical decision making.

Vanessa Lei, Payeng Lor, Vanessa Sanchez, and Kong Choua Thao are 2023 Doctor of Pharmacy Candidates at the Medical College of Wisconsin in Milwaukee, WI. Zachary Hovis is an Assistant Professor at the Medical College of Wisconsin (MCW) School of Pharmacy in Milwaukee, WI.

PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Disclosure: The author(s) declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

References

1. WHO Coronavirus Disease (COVID-19) Dashboard in the United States of America. World Health Organization. Accessed January 19, 2022. https://covid19.who.int/region/amro/country/us
2. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance — United States, January 22–May 30, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(24):759-765. doi: 10.15585/mmwr.mm6924e2
3. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *N Engl J Med.* 2022;386(6):509-520. doi:10.1056/NEJMoa2116044
4. Moderna provides clinical and supply updates on COVID-19 vaccine program ahead of 2nd annual vaccines day. Moderna. Published April 13, 2021. Accessed January 23, 2022. https://investors.modernatx.com/news/news-details/2021/Moderna-Provides-Clinical-and-Supply-Updates-on-COVID-19-Vaccine-Program-Ahead-of-2nd-Annual-Vaccines-Day-04-13-2021/default.aspx
5. Rates of COVID-19 cases and deaths by vaccination status. Centers for Disease Control and Prevention. Updated January 21, 2022. Accessed January 23, 2022. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status
6. King WC, Rubinstein M, Reinhart A, Mejia R. COVID-19 vaccine hesitancy January-May 2021 among 18–64-year-old US adults by employment and occupation. *Prev Med Rep.* 2021;24:101569. doi:10.1016/j.pmedr.2021.101569
7. Rates of laboratory-confirmed COVID-19 hospitalization by vaccination status. Centers for Disease Control and Prevention. Updated January 20, 2022. Accessed January 23, 2022. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination
8. Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: a systematic review of literature. *Diabetes Metab Syndr.* 2021;15(6):102329. doi:10.1016/j.dsx.2021.102329
9. First oral antiviral for covid-19, Lagevrio (molnupiravir), approved by MHRA. GOV.UK. Published November 4, 2021. Accessed January 2, 2022. https://www.gov.uk/government/news/first-oral-antiviral-for-covid-19-lagevrio-molnupiravir-approved-by-mhra
10. Coronavirus (COVID-19) update: FDA authorizes additional oral antiviral for treatment

of COVID-19 in certain adults. U.S. Food and Drug Administration. Published December 23, 2021. Accessed January 20, 2022. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain
11. FDA approves first treatment for COVID-19. U.S. Food and Drug Administration. Published October 22, 2020. Accessed January 20, 2022. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19
12. FDA takes actions to expand use of treatment for outpatients with mild-to-moderate COVID-19. Updated January 21, 2022. Accessed January 25, 2022. https://www.fda.gov/news-events/press-announcements/fda-takes-actions-expand-use-treatment-outpatients-mild-moderate-covid-19
13. Elsawah HK, Elsokary MA, Abdallah MS, ElShafie AH. Efficacy and safety of remdesivir in hospitalized Covid-19 patients: systematic review and meta-analysis including network meta-analysis. *Rev Med Virol.* 2021;31(4):e2187. doi:10.1002/rmv.2187
14. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. *N Engl J Med*. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764
15. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis*. 2022;22(2):209-221. doi:10.1016/S1473-3099(21)00485-0
16. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med.* 2022;386(4):305-315. doi:10.1056/NEJMoa2116846
17. Gavriatopoulou M, Ntanasis-Stathopoulos I, Korompoki E, et al. Emerging treatment strategies for COVID-19 infection. *Clin Exp Med.* 2021;21(2):167-179. doi:10.1007/s10238-020-00671-y
18. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med.* 2020;382(25):2411-2418. doi:10.1056/NEJMoa2012410
19. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ.* 2020;369:m1849. doi:10.1136/bmj.m1849
20. Drożdżal S, Rosik J, Lechowicz K, et al. An update on drugs with therapeutic potential for SARS-CoV-2 (COVID-19) treatment. *Drug Resist Updat.* 2021;59:100794. doi:10.1016/j.drup.2021.100794
21. Pourkarim F, Pourtaghi-Anvarian S, Rezaee H. Molnupiravir: a new candidate for COVID-19 treatment. *Pharmacol Res Perspect.* 2022;10(1):e00909. doi:10.1002/prp2.909
22. Fact sheet for healthcare providers: emergency use authorization for Molnupiravir. U.S. Food and Drug Administration. Published December 23, 2021. Updated February 2, 2022. Accessed April 20, 2022. https://www.fda.gov/media/155054/download
23. Malone B, Campbell EA. Molnupiravir: coding for catastrophe [published correction appears in *Nat Struct Mol Biol.* 2021 Nov;28(11):955]. *Nat Struct Mol Biol.* 2021;28(9):706-708. doi:10.1038/s41594-021-00657-8
24. Lee CC, Hsieh CC, Ko WC. Molnupiravir-a novel oral anti-SARS-CoV-2 agent. *Antibiotics (Basel).* 2021;10(11):1294. doi:10.3390/antibiotics10111294
25. European Medicines Agency. Molnupiravir Covid19-MSD - assessment report. Published November 19, 2021. Accessed January 20, 2022. https://www.ema.europa.eu/en/documents/referral/lagevrio-also-known-molnupiravir-mk-4482-covid-19-article-53-procedure-assessment-report_en.pdf
26. Painter WP, Holman W, Bush JA, et al. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. *Antimicrob Agents Chemother*. 2021;65(5):e02428-20. doi:10.1128/AAC.02428-20
27. Sheahan TP, Sims AC, Zhou S, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. *Sci Transl Med*. 2020;12(541):eabb5883. doi:10.1126/scitranslmed.abb5883

1st Annual

CHRIS DECKER
SCHOLARSHIP GOLF OUTING

Recap

First Annual Christopher Decker Golf Outing Recap

by Lynnae Mahaney, BS Pharm, MBA, FASHP, Sarah Sorum, PharmD

The 1st Annual Chris Decker Golf outing was held June 20, 2022 at Nakoma Country Club in Madison, Wisconsin. This outing was established as a fundraising effort to support the Christopher Decker Scholarship Fund for Wisconsin and Iowa pharmacy students. Through the participation of 140 golfers, donations, and sponsorship, the Wisconsin Pharmacy Foundation raised $50,000 for the scholarship fund, matching a seed gift of $50,000 provided by the Decker Family. Thank you so very much to all the players, sponsors, and those who donated to this effort.

The Christopher Decker Pharmacy Scholarship is intended to recognize future pharmacists who emulate Chris's legacy of innovation, collaboration, mutual respect, positivity, and his call to action to be "Difference Makers." The Decker Family provided an initial gift towards the creation of this scholarship in 2021 and the Wisconsin Pharmacy Foundation Board thought a golf outing, golf being one of Chris' great passions, could help support this fund. A huge debt of gratitude goes to the outing planning committee of volunteers who spent MANY hours brainstorming the plan and bringing it to life; Lynnae Mahaney (chair), Prati Wojtal, Dean Gruber, Nick Olson, Matt Mabie, Mike Gillard, John Decker, Steve Rough, and Eric TeDuits. The committee would also like to recognize the hard work of the PSW staff; it was all PSW hands on deck for every aspect of this outing from working directly with the golf course to communications, food and beverage, the silent auction technology and management, and taking care of our sponsors.

Save the date for June 5, 2023 and join us next year for this wonderful golf outing.

Scholarship applications are being accepted through August 1; the Wisconsin Pharmacy Foundation and Iowa Pharmacy Foundation will award a $1,000 scholarship to one recipient at each Wisconsin and Iowa school of pharmacy in 2022.

The legacy of Chris Decker, 'The Difference Maker' lives on!

Lynnae Mahaney is the Senior Director, Pharmacy Accreditation Office of Global Resource Development and Consulting for the American Society of Health System Pharmacists (ASHP) and was the Planning Committee Chair for the 1st Annual Christopher Decker Golf Outing. Sarah Sourm is the Executive Vice President and CEO at the Pharmacy Society of Wisconsin in Madison, WI.

Thank You to Our Sponsors!

Difference Maker

Visante
Transforming Healthcare through Pharmacy™

Leader

Children's Dental Center of Madison, S.C.
MB Insurance
forward pharmacy
Masters Building Solutions
pharmacists mutual Employee Foundation

Supporters

Ron Fitzwater
TJ Johnsrud
Al & Karen Loeb
Ellen Gaffney
Mark Pilkington
Steve Mullinex
Rod Shafer
Tom Temple
Thomas Thielke
Doug Wetrich
Mike Yaktus

Anthony Aiello Family & John Aiello Family
Todd Decker & Laura Decker
University of Iowa Class of 1988

CARE
Concordia University Wisconsin School of Pharmacy
Iowa Pharmacy
MCW Pharmacy School
Morgan Stanley The Forward Group at Morgan Stanley
Wisconsin Association of Hematology and Oncology
WCA Services Inc.
School of Pharmacy University of Wisconsin-Madison
USave Pharmacy
WHCA / WiCAL

Additional Sponsors

ie. Inside Edge Consulting Group

James and Violet Coats

Spotlight

Leadership Spotlight: Dr. Travis Suss

by Makarios Masoad, PharmD

Travis Suss, PharmD, is a medical outcomes and analytics director at Pfizer. He received his PharmD from the University of Wisconsin-Madison School of Pharmacy, then did his residency at the Milwaukee V.A. Hospital, and stayed there for three years. Suss transitioned to Concordia University, where he was a faculty member for 5 years before moving to his current role at Pfizer in June of 2020. Suss says he greatly enjoys this role, and looks forward to continuing to excell in his job and help providers and patients in hospital settings and health systems all over Wisconsin. In his role, he looks for opportunities to connect with health systems across Wisconsin to be able to support their quality and outcomes initiatives, focused on mutually prioritized disease states. Currently, Suss works on helping to support Wisconsin health systems in their efforts to improve health outcomes across a variety of therapeutic areas including atrial fibrillation, VTE, uterine fibroids and COVID-19. Suss believes he's a great fit for this role thanks to his many years of experience as a pharmacist. He works to improve population health outcomes through data analytics support, workflow efficiency insights, disease-state education and communication/sustainability plans. Additionally, he looks for care gaps, and works with health systems to close those gaps. He identifies stakeholders, including people who work within population health field and may have an interest in better understanding their patient populations within specific disease states.

Today's Concerns

Staff shortages are currently a major concern for health systems, requiring them to carefully prioritize quality initiatives and sometimes put off projects of significant interest. Suss looks for opportunities to offer support that might allow health systems to continue pursuing quality and health outcomes initiatives of shared interest in an environment of limited bandwidth and multiple competing priorities.

Future Advice

Suss offers his favorite advice: "More self-reflection, more critical thinking, more open minds." He reminds us that by keeping those three things in mind, we can do our best in any scenario. Suss says that, before pharmacy school, he was less open to taking advantage of new experiences and opportunities that presented themselves, but once he changed his mindset, a whole new world opened to him, and led him to his role today, not only helping patients, but helping health systems improve care from the top down.

Makarios Masoad is a 2022 Doctor of Pharmacy Graduate of Concordia University Wisconsin School of Pharmacy in Mequon, WI.

ROSALIND FRANKLIN UNIVERSITY OF MEDICINE & SCIENCE SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Business Member Spotlight: The Drug Store, Mueller Drugs Inc.

by Rayan Salih, 2023 PharmD Candidate, Lien Lintean, 2024 PharmD Candidate

A unique pharmacy in Jefferson, Wisconsin is going strong, setting high standards for independent pharmacies. "The pharmacy with years of experience," as its slogan goes. The Drug Store has operated since 1899, and has overcome changes and challenges to remain one of the last few independent pharmacies in its community.[1] As pharmacy practice progresses, The Drug Store has found ways to build and adapt to the times and to the people within its community. Although the pharmacy has redesigned itself over the years, a few things remain the same—like its original tin ceiling and stained-glass windows, along with the staff's devotion to serving the community and its residents.[1] During the more recent history of The Drug Store, Joshua Lotz, PharmD, became its fifth owner. Dr. Lotz and his team work hard to keep the pharmacy's traditions alive. Dr. Lotz exemplifies the true meaning of "your local friendly pharmacists," continuing to build trust and establish deep, meaningful relationships with customers.

Day to Day Practice

The Drug Store operates six days a week, Monday to Saturday, from 8:30 a.m. to 5:30 p.m. The staff start their day by processing new prescription orders that have been sent in overnight or from earlier that morning. Throughout the day, Dr. Lotz and the pharmacy technicians are answering phone calls, filling out prescriptions, and ensuring customers are informed about their medications, insurance plans, and vaccinations (especially the COVID-19 vaccine and booster shots).

One unique service that The Drug Store offers is the dispensing of naloxone without a prescription. Naloxone, known by the brand name Narcan, is an opioid antagonist and is usually dispensed in emergency situations due to opioid overdose.[2] The extension of Wisconsin Act 115, expanding Act 200 of 2014, allowed for practitioners to prescribe this medication to pharmacies under a standing order.[3] This standing order enables "pharmacists to deliver opioid antagonists to individuals at risk for opioid overdose or to an individual in a position to assist an individual at risk for an overdose." This law has allowed the people of Wisconsin greater access to a lifesaving medication. As one of the earlier pharmacies to participate in the state's standing order, The Drug Store has helped local pain management doctors and other local facilities. The process to receive naloxone is as simple as filling out a form that is later processed through the patient's insurance or out of pocket. Although the process is simple, Dr. Lotz and his team have taken steps to ensure that patients are well educated on the medication. Each time naloxone is dispensed, the patient is given forms to fill out and reading materials that contain pertinent education information about the drug. This is one of the unique ways that The Drug Store is helping its community combat the opioid crisis.

Bumps in the Road

Over the years, The Drug Store has faced many obstacles. With the recent ownership transition, Dr. Lotz had to take on the role of business owner, essentially learning business 101. Many pharmacists graduate without prior access to learning how an independent pharmacy operates. Dr. Lotz says how appreciative he has been of his staff, his customers, and the overall response from his community. They welcomed him with open arms, sharing not only their expertise in the pharmacy, but also stories of how the pharmacy used to be back in the day. However, within the past two years, The Drug Store has faced a much heavier burden from the COVID-19 pandemic. Initially, Dr. Lotz, like many others, was uncertain of just how devastating the virus was. As the number of deaths continued to skyrocket in 2020, Dr. Lotz and his team began to implement COVID-19 safety guidelines as soon as they were announced by authorities. With the assistance of a Pharmacy Society of Wisconsin grant, Dr. Lotz was able to fund supplies that met the COVID-19 social distancing guidelines. Gradually, the pharmacy transitioned to relatively more optimal care for their patients and staff. At the time, due to high demand for plexiglass separators, The Drug Store had decided to operate its business outdoors until the glass separators were installed. This brought a new era of changes for the pharmacy, which offered drive-through pickup and curbside vaccinations. With the pandemic running at an all-time high, the number of prescription deliveries to their customers also nearly doubled in a short amount of time. In addition, the number of vaccinations had significantly increased as well. Although curbside services are a new addition to the pharmacy, Dr. Lotz plans to continue implementing these services for his customers, especially for his elderly patients, since they have voiced their appreciation and enjoyment of the service.

Raising the Bar

There are many reasons why this local, independent pharmacy is gaining popularity within its community. The Drug Store is one of the few pharmacies that doesn't use an automated/pre-recorded phone answering system. Patients appreciate the simplicity of calling into their local pharmacy and speaking to a live person right away, versus the mainstream automated systems used by many pharmacy chains. The Drug Store also prides itself on building trust and establishing deep and meaningful relationships with its customers. The staff have set a goal to recall and to know their patients on a first-name basis. Many customers like the personalized and fast services that The Drug Store offers. The pharmacy has seen many customers switch

over to them, because other pharmacies are often under-staffed, and people like being able to come in and leave quickly. Another service Dr. Lotz and his team offer is providing assistance with insurance plan selection. The extra help from Dr. Lotz and his team allows their customers to utilize the pharmacy's services without being compromised in coverage. This is important for many, because certain insurance plans will not cover certain pharmacies, and so, Dr. Lotz works together with his customers to choose a plan that fits. In addition, they also offer unit dose packaging, delivery, and a combination of services that other pharmacies do not offer together.

And although Dr. Lotz and his team are now providing great services to the community, he notes that independent pharmacy was not his first career choice. Lotz says, "Independent pharmacy is not where I had the intention of ending up. I wanted to go into the pharmacy administration route, and when that did not work out, I heard of this job opening from a friend of a friend. At the end, I liked the personalized level that is unique to independent pharmacy." He encourages new pharmacists to participate in a rotation or similar exposure at an independent pharmacy.

Moving Forward

The Drug Store is always finding ways to improve while keeping the people they care for close to heart. They are looking to invest in services to transform their pharmacy into a one-stop shop. About a year ago, Dr. Lotz became certified to offer testing services such as an A1C test, an influenza test, and many more. He is looking to start offering e-care plans as part of the medication therapy management plan, and recently switched to a new pharmacy software that is much more user friendly. In addition, the pharmacy is also a part of the Community Pharmacy Enhanced Services Network, which fosters relationships between healthcare providers and pharmacies to better coordinate a patient's care plan. Dr. Lotz hopes that, with all the new transitions, he can focus more on improving the quality of services within The Drug Store to create a memorable experience for his staff and customers. Lotz says to pharmacy students, "In my position as an owner, there are a whole lot of other things that you have to learn along the way like financials, marketing, and HR, and all of these other little things you are not taught in pharmacy school. Hence, again, one of the best things you can do for yourself would be to do a rotation at [an independent pharmacy]. This is a good way to gauge to see if this is the route for you. If you are not able to get an opportunity to rotate, intern, or work at an independent pharmacy, I would suggest going into one and asking to talk to the owners and pharmacists. Generally, owners and pharmacists that I have talked to would be happy to take some time out of their day to explain what they do."

Lotz cites a recent example of inter-pharmacist helpfulness. "During the rush of COVID-19 vaccines when we got our new pharmacy software, a pharmacist from a different pharmacy spent a couple of hours showing me things that I did not know the software did. It is a good community of independent pharmacists that want to see each other succeed."

Rayan Salih is a 2023 Doctor of Pharmacy Candidate and Lien Lintean is a 2024 Doctor of Pharmacy Candidate at Rosalind Franklin University of Medicine & Science School of Pharmacy in North Chicago, IL.

Disclosure: The author(s) declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

References

1. Store History. The Drug Store Mueller Drugs. Accessed December 2021. https://www.thedrugstoremuellerdrugs.com/history.php
2. Wiersma L. Use of Naloxone. DCC Administrative Directive. Published November 2019. Accessed December 2021. https://doc.wi.gov/GuidanceDocumentsV2/DCC/AD%2021-03%20Use%20of%20Naloxone.pdf
3. Department of Health Services. Statewide naloxone standing order for pharmacists. Published August 2021. Accessed December 2021. https://www.dhs.wisconsin.gov/forms/f01802.pdf

Protect your Tomorrow with VISTA

Our VISTA business package policy protects your tomorrow with:

- Commercial Liability
- Cyber Liability
- Sexual Misconduct and Physical Abuse
- Employment Practices Liability
- Pharmacy Professional Liability
- Commercial Property
- Coverage Enhancements

Additional Coverage Options

- Pharmacist Professional Liability
- Pharmacy Technician Professional Liability
- Workers' Compensation
- Commercial Auto
- Commercial Umbrella
- Executive Liability including:
  - Directory and Officers Liability
  - Employment Practices Liability
  - Fiduciary Liability
- Surety and Fidelity Bonds
- Life - Business and Personal Coverage
- Group Disability

pharmacists mutual™

TOMORROW. IMAGINE THAT.

Professional | Commercial | Personal | Life & Disability

LEARN MORE AT:

phmic.com/vista-pharmacy

phmic.com

Executive Liability, Surety and Fidelity Bonds, Life, and Disability insurance are written through PMC Advantage Insurance Services, Inc., a wholly-owned subsidiary of Pharmacists Mutual Insurance Company.