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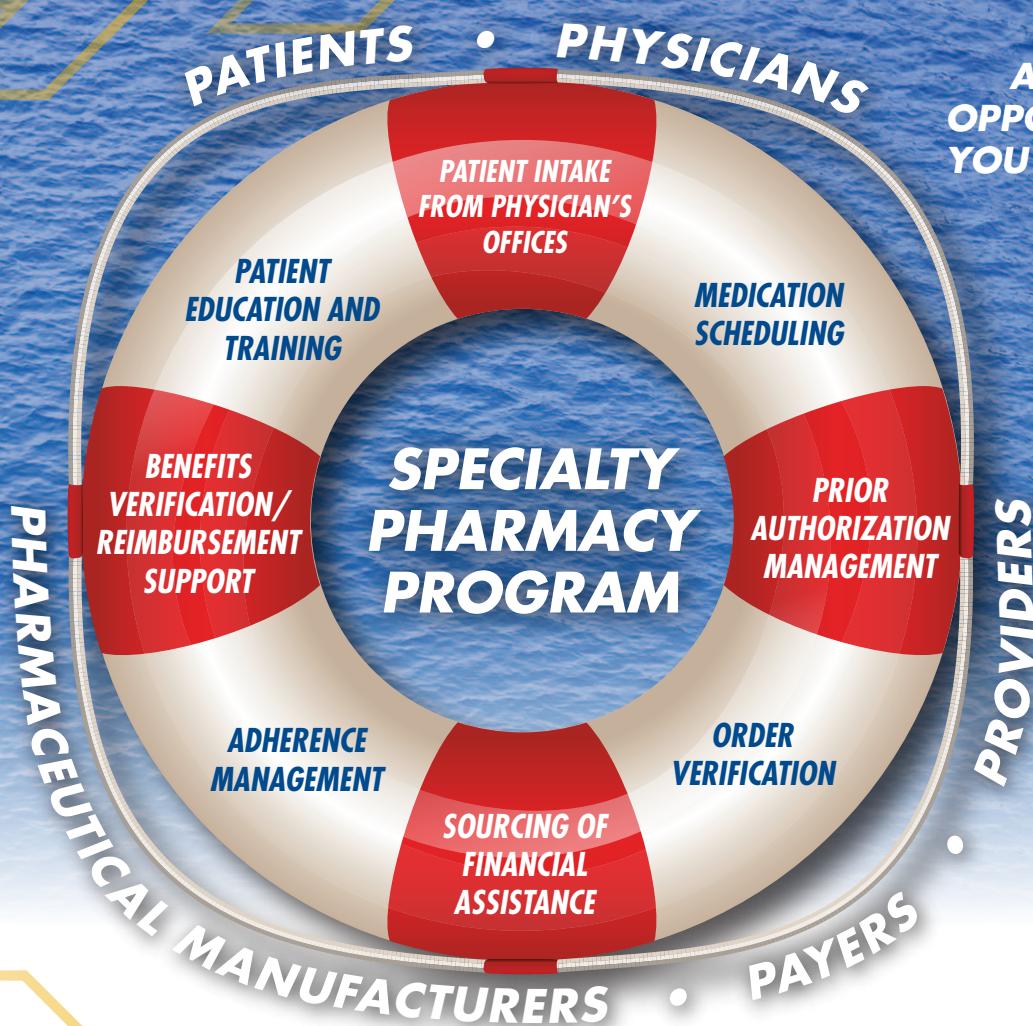


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Mission Statement:

To advance the profession of pharmacy, enabling our members to provide optimal care to those they serve.

President's Letter

One Profession, One Voice.

Hi Everyone! Wow, we accomplished so much in the first half of the year. With all of the continuing education programs we ran and certificate courses it was hard to come up for fresh air, but our social committee managed to host our first ever +TONIC event. It was such a refreshing break to see you all for something outside of an educational program. A group of us met in Long Branch for a happy hour and networking evening that was one for the books! If you could not make it, do not worry there will be plenty of more in the future! Great things are happening and it takes YOU to make them amazing!

In the first half of the year, the leadership has continued to make several legislative accomplishments – attending several important Assembly and Senate committee hearing on biosimilars, medication synchronization, and MAC transparency to name a

few. NJPhA also hosted another pharmacy conference, and attended a variety of meetings throughout the State – Board of Pharmacy, Department of Health, the New Jersey Immunization Network, and others—and the summer doesn't look like it will slow down! Remember, NJPhA is the only organization that lobbies on behalf of ALL pharmacists in the State of New Jersey – spread the word, tell your friends!

I can't wait to see you all at the Annual Meeting and Convention in October! Let's continue making strides for our Profession!

Sincerely,
Moriah
Moriah J. Weissman, PharmD, CCP
NJPhA President

Message from the Convention Chair

FINDING BALANCE...Past, Present, Future

I am proud to announce the 145th year of our annual convention on October 16-18, 2015 at Harrah's in Atlantic City! This will be an exciting time as we will honor NJPhA past presidents, how they shaped our profession, where we stand today and how we move forward. Be sure to enjoy our display of historic NJPhA memorabilia.

As we are still planning many great things, I'll share at this time that continuing education activities will begin on Friday , starting with two certificate programs at noon. Our regional presidents and committee round table meetings will also be held in the afternoon. All members are welcome to get more involved by attending the roundtable sessions in their region or getting more involved in a committee! The day will finish off with a relaxing Welcome Gathering.

Informative continuing education, student, certificate programs and the annual meeting await you on Saturday! We are working very closely with exhibitors by having them engaged in activities and plan a fun-filled theme 'Boardwalk Bash' on Saturday night. This will include reception, games, prizes, and exhibits as we dance the evening away.

On Sunday, exhibits, CE and certificate programming follow breakfast. We are so fortunate to have Michael R. Cohen, RPh, MS, ScD (Hon), DPS (Hon), FASHP, President of the Institute

for Safe Medication Practices as our keynote speaker this year. After installation luncheon and awards presentation, we will have an educational law program and wrap up.

On behalf of NJPhA leadership, I encourage you to celebrate our past leaders, contribute in meetings, obtain credits and, have fun... as we find balance.

Professionally yours,
Ruth Marietta, RPH, CCP
First Vice President & 2015 Convention Chair



Message from the BOT Chairman

Dear NJPhA Members,

Welcome to our Spring Journal! I hope you are enjoying the warmer weather and have some fun summer plans ahead of you. Most of all, I hope you have already blocked your calendar for yet another fabulous NJPhA convention. October is still a beautiful time of the year at the Jersey Shore and this year's event, from 16-18 October at Harrah's Hotel and Casino will be the best one yet. Please take the time to submit candidates for NJPhA Awards (it's all online and very easy) so that we can continue to recognize the best in our profession. Finally, we'll be voting for our next 2nd VP in the coming weeks - please keep your eye out for that email and be sure to participate.

As always, there is a lot going on - in our profession and at NJPhA. More involvement by members is appreciated and welcome. Feel free to reach out to me or any line officer, board of trustee member or regional officer to learn more.

Wishing you a safe and happy summer.

Carrie Corboy, RPh, PharmD, CCP

From The Editors' Desk...

Dear Colleagues,

We hope that everyone is transitioning into summer 2015! The NJ Journal of Pharmacy – the official peer-reviewed journal of the NJ Pharmacists Association is pleased to provide an issue dedicated to cardiovascular disease. This issue will introduce two new medications. One is a novel drug , ivabradine, that is an IF channel blocker, the first in its class approved in the United States by the FDA, the other, Edoxaban is a new Factor Xa inhibitor. Earn continuing education by completing and submitting one or both of the CE activities: pulmonary hypertension and JNC8. We also offer an article on aspirin use in cardiovascular disease. Our Pharmacy Practice Spotlight highlights the amazing experience of a pharmacist's mission to Kenya.

retail, hospital and hospice and palliative care. My full time employment is as a clinical pharmacist in hospice and palliative care. In my tenure at my place of employment, among many roles, I served as part of a medication therapy committee. Through a collaborative effort select pharmacists within the company helped to write drug monographs that helped medical practitioners including prescribers, physicians, nurse practitioners, prescriber assistants and nurses make medication therapy choices for patients on hospice based on symptom and disease management, helping to maintain medication costs for hospices. I served for several years as the Editor-in-Chief for our nationally recognized manual of formulary medications.

The theme of the next issue is dermatology, followed by nutrition/GI. Please consider becoming active in the development of the NJ Journal of Pharmacy, through either submission of an article, or becoming a peer-reviewer. If interested please reach out to me, Maria Leibfried, Elise Barry, or one of the NJPhA officers. You may email ideas and submissions to leibfried2@hotmail.com or marcella.r.brown@gmail.com. We can help you with a topic consideration for the journal.

We also are happy to introduce the Marcella R. Brown to the editorial staff! Please learn more about Marcella.

Most recently, I have served as a volunteer peer-reviewer for The Consultant Pharmacist and our esteemed NJ Journal of Pharmacy. I currently serve, part-time, as an adjunct professor at Harcum Junior College in Philadelphia and in the past taught as a Palliative Care Elective Course Instructor at the University of the Sciences'. In this new role as a co-editor for the NJ Journal of Pharmacy, I will work closely alongside of Maria Leibfried continuing to promote great pharmacy practice, introducing new medications and concepts of disease state management, exciting spotlights on community practice and emphasizing medication therapy management among many other themes to our many readers. I have confidence that together we will continue to make the NJ Journal of Pharmacy a must-read! We hope to continue to steadily expand our network of reviewers and authors and hope that you will become involved!

On behalf of everyone that makes the NJ Journal of Pharmacy great, I look forward to this opportunity to work with our writers, readers, subscribers, and contributors on focusing on our dynamic practice of pharmacy and all of the many changes it brings!

Professionally,
Marcella

Dear friends,
My name is Marcella Brown and I am delighted to introduce myself as a co-editor for the NJ Journal of Pharmacy. Over the years I have worked in many different aspects of pharmacy, including

The Use of Aspirin for Primary Prevention of Cardiovascular Disease

by Asha Gupta, PharmD, R.Ph

Background

Coronary and cerebrovascular events are a leading cause of death worldwide. These events are a result of thrombus formation, caused by atherosclerotic plaque rupture or embolism and platelet aggregation. While age is the strongest predictor of cardiovascular disease (CVD) risk, other contributing factors include sex, cholesterol (total and HDL), blood pressure and use of treatment, diabetes status and smoking status; all of which are components in the 10-year risk estimator launched by the American College of Cardiology (ACC) and the American Heart Association (AHA) in 2013.¹ The AHA estimated the financial burden of CVD to be an annual direct and indirect cost of \$523 billion in the United States (US). It is projected that by 2030, 40.8% of the US population will have some form of CVD, and the annual cost will increase to \$1.13 trillion. These strong trends suggest the need of primary prevention for patients with risk factors for CVD.^{2,3}

Several guidelines recommend aspirin (ASA) for secondary prevention of CVD events, for example, a previous event of non-ST and ST elevation myocardial infarction (NSTEMI and STEMI), however the use of aspirin for primary prevention is still controversial.⁴⁻⁶ The concern is that the benefit of inhibiting thromboxane, and therefore, platelet aggregation, with ASA in patients without risk factors for CVD may not outweigh the risk of serious adverse effects (gastrointestinal, renal and cardiovascular).⁶ This article serves to summarize the recent findings that evaluated the use of aspirin for the prevention of CVD in different adult populations with preexisting comorbidities (diabetes mellitus, chronic kidney disease, human immunodeficiency virus (HIV)).

Current Aspirin Use Recommendations

	2009 US Preventive Services Task Force: Aspirin for the Prevention of Cardiovascular Disease^{a,b}		2014 AHA/ASA Guidelines for Primary Prevention of Stroke
Men, Age 45-79	Aspirin use recommended if reduction in MI outweighs potential harm due to an increase in GI hemorrhage	10-year Framingham Risk Score	<ul style="list-style-type: none">>10% – Aspirin use for cardiovascular prophylaxis (including but not specific to stroke) is reasonable<10% – Aspirin is not useful in preventing first stroke
Women, Age 55-79	Aspirin use recommended if reduction in ischemic stroke outweighs potential harm due to an increase in GI hemorrhage	Women	<ul style="list-style-type: none">Aspirin (81 mg daily or 100 mg every other day) may be helpful, even in women with diabetes
Men and Women, 80 Years and Older	Insufficient evidence to assess the balance of benefits and harms of aspirin use for CVD prevention	Diabetes Mellitus	<ul style="list-style-type: none">Aspirin is not useful in patients with diabetes in absence of other high-risk conditionsNot useful for prevention of first stroke in patients with diabetes and asymptomatic PAD^c
Women Younger than 55 (Stroke), Men Younger than 45 (MI)	Aspirin use is not recommended	Chronic Kidney Disease	<ul style="list-style-type: none">Aspirin use might be considered in patients with CKD (eGFR <45 mL/min)Aspirin not recommended for severe kidney disease (Stage 4 or 5, eGFR <30 mL/min)

^aThese recommendations apply to adult men and women without a history of coronary heart disease or stroke.

^bNew recommendations in progress.

^cCilastazol may be reasonable for prevention of first stroke in patients with PAD.

AHA = American Heart Association, ASA = American Stroke Association, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, GI = gastrointestinal, PAD = peripheral artery disease.

Sources: U.S. Preventive Services Task Force. Website.⁷; Kernan 2014.⁸

Aspirin Efficacy in Primary Prevention of Cardiovascular Disease

A meta-analysis of nine well-designed, randomized controlled trials involving 102,621 eligible participants found that aspirin use was associated with a significant 10% reduction in risk of total CVD events (OR, 0.0; 95% CI 0.85–0.96) and a 20% risk reduction in nonfatal MI (OR 0.80; 95% CI, 0.67–0.96), however there was no beneficial effect on fatal MI, stroke, or CVD death. In contrast, there was a 70% excess risk of total bleeding events (OR, 1.7; 95% CI, 1.17–2.46) and a higher than 30% excess risk of nontrivial bleeding events (OR, 1.31; 95% CI, 1.14–1.50). Other important findings include that there was no significant difference between male or female patients, although aspirin may be metabolized differently, the risk of CVD events was lower in older people, while younger people and people with high blood pressure experienced more nontrivial bleeding.⁹

Aspirin Efficacy in Select Patient Populations

Women

Aspirin is commonly used for the prevention of myocardial infarction (MI) and cardiovascular disease (CVD) in women; however, there is limited randomized evidence suggesting that aspirin has a modest effect on total CVD. The Women's Health Study was a randomized trial which estimated the effect of continuous use of aspirin (100 mg or placebo every other day) in 39,876 health female health professionals who were 49 years and older. The women were randomly assigned to receiving either aspirin 100 mg or placebo, which was administered every other day. Results from the as-treated analyses showed a slight reduction in CVD mortality (HR=0.88, 95% CI=0.67–1.16). Results using the marginal structure model, which adjusted for non-compliance, showed similar total CVD (HR=0.93; 95% CI: 0.81, 1.07), but showed lower CVD mortality with aspirin use (HR = 0.76; 95% CI: 0.54, 1.08). Overall, the use of continuous aspirin shows potential benefit for CVD mortality, but has limited efficacy on total CVD in women.¹⁰

Elderly Population

While CVD-associated death rate has decreased over the years, it remains the highest among those aged 65 years and over. By 2030, it is estimated that the persons >65 years will be >20% of the US population, therefore, as “baby-boomers” age, the potential for CVD prevention is even greater.¹¹

A double-blind, randomized, placebo-controlled, on-going study, ASPirin in Reducing Events in the Elderly (ASPREE), aims to determine whether the preventative benefits of low-dose aspirin outweigh the risks in 19,000 healthy subjects aged 65 years and older. Patients will be randomly assigned to receive daily oral 100 mg enteric-coated ASA or placebo and will be assessed for the primary endpoint of disability-free life including: onset of dementia, total mortality, or persistent disability. The anticipated completion date of this study is December 2018.¹²

The Physicians' Health Study was a randomized, double-blind, placebo-controlled trial which monitored a cohort of predominantly Caucasian male physicians aged 40–84 years, over a span of 24 years, to evaluate the relationship between the control of four modifiable risk factors [smoking, non-HDL-C, blood pressure, and aspirin use] and risk of cardiovascular disease in pri-

mary prevention. The results for 4182 subjects aged > 65 years old, when compared to the time 4 of 4 risk factors were controlled (6.0% of participants), control of 0 of 4 risk factors almost quadrupled CVD risk (0.4% of participants; event rate 41.2%; HR 3.83, 95% CI 1.72–8.55); control of 1 of 4 risk factors more than double the risk (14.2% of participants; HR 2.53, 95% CI 1.80–3.57); control of 2 of 4 risk factors almost doubled risk (43.8% of participants; HR 1.94, 95% CI 1.41–2.69), and those with control of 3 of 4 risk factors also were at increased risk (35.6% of participants; HR 1.80, 95% CI 1.30–2.50). Control of each additional risk factor was associated with greater cardiovascular protection ($P=0.002$). Overall, the study showed that with aggressive risk factor management, there was substantial protection against incidence of CVD in older men.¹³

Diabetes Mellitus

Patients with diabetes are at a two-fold increase in risk of CV events due to accelerated atherosclerosis and inflammation. Furthermore, for every unit increase in HbA1c, the risk for MI increases by 16% and the risk for CVD mortality increases by 20% for each 1% increase in HbA1c. In addition, studies suggest that diabetics may require higher doses of aspirin due to high platelet turnover and incomplete thromboxane inhibition.¹⁴

In a meta-analysis of 14 trials (107,686 participants), aspirin therapy was associated with reductions in major cardiovascular events (risk ratio, 0.90; 95% confidence interval, 0.85–0.95), myocardial infarction (0.86; 0.75–0.93), ischemic stroke (0.86; 0.75–0.98) and all-cause mortality (0.94; 0.89–0.99). However, there were also increases in hemorrhagic stroke (1.34; 1.01–1.79) and major bleeding (1.55; 1.35–1.78). The number needed to treat (NNT) to prevent 1 major cardiovascular event was 284, over a mean follow-up of 6.8 years. By comparison, the numbers needed to harm (NNH) to cause 1 major bleeding was 299. The results of subgroup analyses suggested that aspirin use lead to a decrease in stroke among diabetic women and a decrease in MI among diabetic men, with risk reductions achieved at low doses (75 mg/day) as large as those obtained with higher doses (650 mg/day).¹⁵

Chronic Kidney Disease

Similar to diabetes, patients with preexisting CKD are also at an increased risk of CVD events. Patients with CKD have increased oxidative stress, inflammation, abnormal platelet function, atherosclerosis and an attenuated response to antiplatelet agents. A propensity score (PS) -matched, retrospective analysis in 25,340 patients with CKD (defined as eGFR <60ml/min/1.73m² and the presence of proteinuria on two occasions) found that the risk of atherosclerotic CVD was significantly higher in aspirin users than in non-users in the unmatched cohort (HR, 2.577; 95% CI, 2.238–2.967; $P<0.001$) and matched cohort (HR, 2.259; 95% CI, 1.880–2.714; $P<0.001$). Even with the use of low-dose aspirin for the prevention of CVD in CKD patients, between aspirin users and non-users, there was no significant differences in all-cause mortality or composite bleeding events (gastrointestinal bleeding, hemorrhagic stroke, and hemoptysis) but the risk of doubling of serum creatinine, and renal death risk of was higher in aspirin users. This study demonstrated that the use of low-dose aspirin for protection against CVD in CKD patients can rather increase the risk for CVD and renal progression.¹⁶

HIV

Although, clinicians know that HIV-infected patients have an increased risk of atherosclerosis and CVD-related events (first MI or ischemic stroke), a prospective study found that aspirin was generally underprescribed even in those patients who met the 2009 USPSTF criteria for ASA for primary prevention and were at high risk for events (10-year risk >10%). Patients who had traditional CVD-related comorbidities (diabetes, hyperlipidemia, and smoking) were more likely to receive ASA whereas patients with more advanced HIV (CD4+ cell count <200 cells/L) were less likely to receive ASA since providers were more focused on HIV management than CVD risk reduction. Low utilization of ASA in this complex patient population can be due to the absence of HIV-specific literature, provider unfamiliarity with ASA recommendations for the general population, as well as medical and social problems and patient-provider time constraints.¹⁷

Conclusion

There are several retrospective studies which demonstrate possible benefits of using aspirin for the primary prevention of cardiovascular disease, however, at the risk of adverse effects such as gastrointestinal bleeding. Low-dose aspirin should be recommended on an individual basis, if a patient is at high risk of CVD, with consideration of contributing comorbidities, using a risk estimator. Pharmacists should continue encouraging self-monitoring of blood pressure, medication adherence, and lifestyle modifications, and they should also counsel patients on the cardiovascular, gastrointestinal, and renal adverse effects associated with aspirin use. Results from prospective studies evaluating long-term efficacy and safety of aspirin use, along with disease-specific clinical practice guidelines featuring special considerations for common comorbidities, will transform the prevention and treatment of cardiovascular disease in the forthcoming years.

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Use of Corlanor® (ivabradine) for Chronic Heart Failure

By: Madeline King, PharmD

Introduction

The newest drug for chronic heart failure, ivabradine (Corlanor®), was approved by the FDA in April of 2015 through the FDA's expedited review process, with fast track designation, because of the potential to provide significant improvement over standard therapy in a serious disease.¹ Ivabradine is also available in Europe and is recommended by the National Institute for Health and Care Excellence (NICE) guidelines for use in chronic heart failure, or as a second line or add-on agent for stable angina². Ivabradine reduces heart rate by a novel mechanism and has shown improved outcomes for patients with chronic heart failure in addition to standard therapy. Elevated heart rate is directly related to disease severity and worse outcomes in patients with heart failure³. The rationale for evaluating ivabradine in patients with heart failure is that a reduction in heart rate should improve outcomes.

Pharmacology

Ivabradine inhibits the I_F channel and is currently the only drug in this class to be approved in the US. The I_F channel is controlled by intracellular cAMP and is activated and inhibited by β -adrenergic and muscarinic M2 receptor stimulation, respectively⁴. It plays a major role in spontaneous activity and rate control. Ivabradine is selective for the I_F channel and no other receptors, resulting in a reduction in the rate of sinoatrial node pacemaker cell firing and subsequently, reduction in heart rate without a change in the action potential duration. Its action is concentration-dependent and it enters the channel from the intracellular side. I_F channels must be open for ivabradine to block them, and the magnitude of inhibition is related to the frequency of the channel opening. This indicates that the drug is more effective in higher heart rates.

Ivabradine has no negative inotropic effects, as are seen with β -blockers and calcium-channel blockers. It also has not been shown to result in rebound effects after discontinuation of the drug, or pharmacological tolerance³.

Outcomes

The Systolic Heart failure treatment with the I_F inhibitor ivabradine Trial (SHIFT) evaluated the efficacy of ivabradine in chronic heart failure. Patients evaluated had a heart rate of at least 70 bpm, ejection fraction <35%, and stable, symptomatic chronic heart failure for at least 4 weeks with a previous admission for worsening heart failure in the previous 12 months. Patients with congenital heart disease or primary severe valvular disease were excluded. Patients were randomized to receive ivabradine or placebo. In the ivabradine group 3241 patients were evaluated versus 3264 in the placebo group. Ninety-eight percent of patients in each group had New York Heart Association class II or III heart failure. Dosing of ivabradine was initiated at 5 mg twice daily and adjusted based on heart rate after the first 14 days to 2.5 mg, 5 mg or 7.5 mg twice daily, in addition to appropriate heart failure treatment. Patients receiving ivabradine had a lower rate

of cardiovascular death or hospital admission due to worsening heart failure than those receiving placebo (24 vs 29%, HR 0.82, 95% CI 0.75-0.90, p<0.0001), which was the primary endpoint. The rate of cardiovascular death was not significantly different between groups (p=0.128), but the rate of death due to worsening heart failure was significantly lower in the ivabradine group (HR 0.74, 95% CI 0.66-0.83, p=0.014), as was the rate of all-cause hospital admissions (p=0.003). The overall reduction in heart rate at the end of the study in the ivabradine group was 8.1 bpm (95% CI 7.5-8.7)⁵.

A post hoc analysis of SHIFT investigated ivabradine in patients with severe heart failure; with an ejection fraction of <20% and/or NYHA class IV heart failure. These patients were compared to those with less severe heart failure. Ivabradine did not demonstrate a significant difference with regards to cardiovascular death or hospitalization for heart failure between the groups. It did, however, improve NYHA class in 38 vs 29% of patients overall (p=0.009). Ivabradine significantly reduced the risk of cardiovascular death or hospitalization for worsening heart failure by 25% in patients who had severe heart failure (p=0.045), and a baseline heart rate of at least 75 bpm⁶.

Ivabradine was also evaluated for efficacy in patients with stable angina without heart failure in the Study Assessing the Morbidity-Mortality Benefits of the IF Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY). Patients received between 5 mg and 10 mg of ivabradine twice daily, with doses based on age and heart rate. Patients also continued to receive guideline based therapy for stable angina (i.e. aspirin, statins, beta-blockers, ACE inhibitors). While the addition of ivabradine did not significantly reduce the primary endpoint, there was a significant reduction in heart rate (60.7 ± 9.0 bpm in the ivabradine group versus 70.6 ± 10.1 bpm in the group receiving placebo)⁷.

Discussion

There is evidence that ivabradine has a significant impact on lowering heart rate, and improves outcomes in patients with heart failure, with an 18% reduction in the rate of cardiovascular death or hospital admission for worsening heart failure in patients receiving ivabradine in addition to evidence-based therapy. Patients who had a higher baseline heart rate derived more benefit from ivabradine therapy than those who had heart rates lower than the median. In patients with stable angina but who did not fall into a NYHA classification for heart failure, the same benefit was not seen. In this population, although heart rate was significantly reduced in patients receiving ivabradine versus placebo, there were no significant differences in the targeted outcomes between groups. The SHIFT study only evaluated patients in normal sinus rhythm who were already on background therapy for heart failure, so results shouldn't be extrapolated to other populations. Overall, ivabradine was well tolerated, with very few patients discontinuing the drug

due to bradycardia or other adverse events. In conclusion, ivabradine appears to be beneficial in patients with chronic heart failure, as an add-on therapy to lower heart rate, and can be considered in select patients who have not responded to current therapy.

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JNC8 Evidence-Based Guidelines for Management of Hypertension in Adults:

What Pharmacists Need to Know

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Learning Objectives:

After participating in this activity, the participant shall be able to:

Pharmacist:

1. describe JNC8 guidelines
2. list treatment goals for JNC8
3. list treatment options for hypertension

Pharmacy Technician:

1. define JNC8
2. identify treatment options for hypertension

Author disclosures: none

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Release Date : 07/06/2015 Expiration: 07/06/2018

CEU Hours: 1 contact hour of continuing education credit (0.1 CEU)

Introduction

Hypertension is a serious medical condition, which can lead to life-threatening complications if left untreated, such as stroke, myocardial infarction (MI), heart failure, cardiac arrhythmias, and renal failure. It is estimated that approximately 78 million U.S. adults (20 years of age and over) had high blood pressure in 2010 with approximately half inadequately controlled. Seventy percent of adults 65 years of age and over have hypertension. In the same year, hypertension was the primary or contributing cause of death in over 2.5 million people. The direct and indirect costs associated with hypertension totaled \$46.4 billion in 2010.¹ There are various classes of antihypertensive agents available as first-line treatment of hypertension, which includes the following: angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide diuretics. The decision on which agent to initiate first, how to adjust therapy, and target blood pressure goal depend on patient characteristics and risk factors.² With hypertension still being the primary cause of morbidity and mortality, along with its association with high costs in healthcare, there is a need for improvement in management of this disease state. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) was released nearly 10 years ago. In 2013, the much anticipated Eighth Joint National Committee (JNC8) guidelines were published. The National Heart, Lung and Blood Institute (NHLBI) appointed the JNC8 committee to establish evidence-based recommendations for blood pressure targets and hypertension treatment to provide guidance for clinicians. In 2013, NHLBI discontinued participation in development of JNC8 guidelines and instead partnered with selected organizations including the American College of Cardiology and American Heart Association to develop separate guidelines anticipated to be released in 2016. The purpose of this review is to provide the clinician with a summary of JNC8 guideline recommendations.

Methodology

Evidence review was limited to randomized controlled trials (RCTs). The evidence review included studies of adults 18 years of age or older with hypertension as defined by the study, usually systolic blood pressure (SBP) greater than or equal to 140 mmHg, diastolic blood pressure (DBP) greater than or equal to 90 mmHg, or both. Prespecified subgroups included patients with diabetes, coronary artery disease, peripheral artery disease, heart failure, previous stroke, chronic kidney disease (CKD), proteinuria, older adults, men and women, racial and ethnic groups, and smokers. Pilot studies, studies with a sample size less than 100, and studies with a follow-up of less than one year were excluded. Systematic reviews and meta-analyses previously published were also excluded in the evidence review as the Panel conducted its own systematic review of original studies. Search dates for the literature review spanned from January 1, 1966 to December 31, 2009 with two independent searches of PubMed and CINAHL between December 2009 and August 2013. Only studies that measured the following outcomes were included by the Panel: overall mortality; mortality related to CVD; mortality related to CKD; MI; heart failure; hospitalization for heart failure; stroke; coronary revascularization; peripheral revascularization; end stage renal disease; measuring the serum creatinine concentration doubling; or measuring the estimated glomerular filtration rate being reduced in half. Only studies rated as "Good" or "Fair" using NHLBI's standardized quality rating tool were included. Evidence statements were graded for quality as "High, Moderate, or Low." Recommendations were graded as Grade A (Strong Recommendation), Grade B (Moderate Recommendation), Grade C (Weak Recommendation), Grade D (Recommendation Against), Grade E (Expert Opinion) or Grade N (No Recommendation).²

Limitations

JNC8 does not represent a comprehensive guideline for hypertension; rather, this evidence-based guideline addressed three specific questions related to management of high blood pressure: (1) whether initiating therapy at specific blood pressure thresholds improves outcomes in adults; (2) whether treatment to a specified blood pressure goal improves outcomes; and (3) whether antihypertensive drugs or drug classes differ in benefits and harms on health outcomes. The evidence review excluded observational studies, systematic reviews, and meta-analyses, and RCTs that enrolled pre-hypertensive or non-hypertensive individuals were excluded. Of note, many studies included in the review were conducted when risk of cardiovascular morbidity and mortality were greater than today; thus, overestimation of effect sizes is possible. In addition, medication costs and treatment adherence were not evaluated in this guideline. In the absence of high-quality evidence, the panel used fair-quality evidence and panel members' experiences for recommendations. Unlike previous JNC reports, this guideline was not endorsed by a professional society or federal agency before publication.²

Blood Pressure Goals and Thresholds for Treatment Initiation

For the general population 60 years of age and older, pharmacotherapy should be initiated for SBP \geq 150 mmHg or DBP \geq 90 mmHg. The goal of such therapy is to maintain blood pressure below 150/90 mmHg (Table 1). Based upon the results of three large trials, maintaining blood pressure (BP) $<$ 150/90 mmHg reduces cerebrovascular morbidity and mortality (Evidence Quality: High), fatal and nonfatal heart failure (Evidence Quality: Moderate), and coronary heart disease (CHD) (Evidence Quality: Moderate).²⁻⁵

A lower SBP target of $<$ 140 mmHg, previously recommended in JNC7, was compared to $<$ 150 mmHg in two trials which included elderly Japanese patients with hypertension.^{6,7} Another trial compared a lower target of $<$ 130 mmHg to $<$ 140 mmHg in non-diabetic adults who are 55 years of age and over.⁸ None of these three trials showed a significant difference in health outcomes; therefore, these lower targets were not recommended by the guidelines. Patients already titrated to lower BP goals based upon past guideline suggestions, as well as new

patients who maintain lower SBP (< 140 mmHg) do not require readjustment of therapy to the new higher goal if therapy is well tolerated (Grade E).

For patients less than 60 years of age, it is recommended to initiate therapy when DBP \geq 90 mmHg to achieve a target DBP of < 90 mmHg (Grade A). The evidence for patients between the ages of 30 and 59 comes from five large trials showing a reduction in cerebrovascular events, heart failure, and mortality.⁹⁻¹³ For patients between the ages of 18 and 29, despite a lack of evidence to describe any potential benefit on health outcomes, the panel provides the same recommendation of lowering DBP to < 90 mmHg (Grade E). JNC8 recommendations for SBP goal for the general population under 60 years of age was preserved at < 140 mmHg due to the lack of evidence in comparison to other goal ranges (Grade E).

Table 1. Comparison of JNC7 and JNC8 Guidelines

	JNC7	JNC8
Definitions	Optimal: < 120/80 mmHg Normal: 120-129/80-84 mmHg Borderline: 130-139/85-89 mmHg Hypertension: \geq 140/90 mmHg Stage 1: 140-159/90-99 mmHg Stage 2: 160-179/100-109 mmHg Stage 3: \geq 180/110 mmHg Blood pressure is disease specific only	Definitions not addressed, but blood pressure treatment goals and thresholds defined Blood Pressure is age-dependent and disease specific
Treatment Goals	General population: < 140/90 mmHg	General population \geq 60 years: < 150/90 mmHg General population < 60 years: < 140/90 mmHg
	Diabetes: < 130/80 mmHg	Diabetes: < 140/90 mmHg
	CKD: < 130/80 mmHg	CKD: < 140/90 mmHg
Pharmacologic Therapy	Thiazide-type diuretics as initial therapy for patients without compelling indications, but all 5 classes of antihypertensives could be considered For patients with diabetes, CKD, heart failure, myocardial infarction, stroke, and high CVD risk specific recommendations from the respective societies	4 drug classes recommended: ACEI, ARB, CCB or thiazide-type diuretics Beta blockers are not recommended for patients with no compelling indications Recommended specific medication classes based on evidence review for racial, CKD, and diabetic subgroups

Treatment Recommendations

Initial treatment for the general non-black population should include a thiazide-type diuretic, CCB, ACEI, or an ARB (Grade B) (Figure 1). These four drug classes have been shown to have comparable benefits on cerebrovascular, cardiovascular, and renal outcomes. In the general population 55 years of age and older, the two drug classes that have demonstrated significant benefit over CCBs as initial therapy for improving heart failure outcomes are thiazide diuretics (Evidence Quality: Good) and ACEIs (Evidence Quality: Moderate). While this information should be utilized in clinical decision-making, it was not considered a reason to remove the other agents from the

recommendation. In the general population, lowering BP is considered more important than use of a specific agent.

Beta-blockers are not recommended for initial therapy due to the Cardiovascular Morbidity and Mortality in the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study proving them inferior to ARBs in preventing cardiovascular death, MI, and stroke (Evidence Quality: Low).¹⁴ Several other trials found inconclusive results when comparing beta-blockers to other drug classes; therefore, beta-blockers are only to be used after other recommended therapies have been unsuccessful. Alpha-blockers are not recommended for initial therapy due to evidence from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial, in which the doxazosin treatment arm was terminated early due to greater incidence of combined cardiovascular outcomes compared to the thiazide diuretic chlorthalidone.¹⁵ JNC8 guidelines do not recommend the following drug classes for initial therapy due to the lack of good or fair quality evidence supporting their use: alpha₁/beta-blockers; vasodilating beta blockers; central alpha₂-adrenergic agonists; direct vasodilators; aldosterone receptor antagonists; peripherally acting adrenergic antagonists; and loop diuretics.

Most patients will require more than one antihypertensive agent to maintain their BP goal. If BP remains uncontrolled after one month of therapy with one of the recommended initial agents, the guidelines recommend either an increase in dose or the addition of a second agent. A second agent should be chosen from one of these remaining recommended drug classes: thiazides; CCBs; ACEIs; or ARBs. It is important to note that ACEIs and ARBs should not be used concomitantly in the same patient due to increased risk for adverse effects. If after another month of follow-up the patient still is not controlled, a third agent from the recommended drug classes should be added to the regimen. If a patient still has not achieved the target blood pressure, other antihypertensive agents may be utilized. Either the presence of intolerable adverse effects of any medication class or the failure of a medication to elicit an effect is an acceptable reason to discontinue the agent and initiate a suitable replacement. Clinicians should follow-up with the patient to ensure the goal blood pressure range is maintained and to encourage healthy lifestyle choices.

Treatment Recommendations for Subpopulations

Chronic Kidney Disease

Guideline recommendations include initiating pharmacologic treatment to lower SBP \geq 140 mmHg or DBP \geq 90 mmHg to goal BP $<$ 140/90 mmHg for patients 18 years of age and older with CKD (Grade E). There is insufficient evidence to suggest that a lower blood pressure goal (for example, $<$ 130/90 mmHg) compared with a goal of $<$ 140/90 mmHg from treatment with antihypertensive drug therapy confers a benefit for mortality or cardiovascular health outcomes or slows the progression of kidney disease. The JNC8 guidelines suggest that antihypertensive treatment be individualized for people aged 70 years or older with estimated glomerular filtration rate less than 60 mL/min/1.73m² while considering factors such as frailty, comorbidities, and albuminuria. Evidence supporting a specific goal blood pressure in patients 70 years of age or older with CKD is lacking.²

Patients with CKD should be initiated on an ACEI or ARB (Grade B). JNC8 recommendations support the use of ACEI or ARB in patients with CKD regardless of race or diabetes status based on improvement in kidney outcomes for patients with CKD. This recommendation applies to CKD patients regardless of presence of proteinuria. The African American Study of Kidney Disease and Hypertension Study Group (AASK) demonstrated improved kidney outcomes in African American patients with CKD when treated with an ACEI.¹⁶

In comparison, the Kidney Disease Improving Global Outcomes Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease recommends that adults with CKD, in the absence of proteinuria whose BP is consistently > 140 mmHg systolic or > 90 mmHg diastolic, be treated with an ACEI or ARB to a goal blood pressure $\leq 140/90$ mmHg. The guidelines recommend that patients with CKD with proteinuria whose SBP is consistently > 130 mmHg or DBP > 80 mmHg be treated with an ACEI or ARB to a goal BP of $\leq 130/80$ mmHg.¹⁷

Diabetes

For patients with diabetes and with either a SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, pharmacologic treatment should be initiated to lower BP to a goal of $< 140/90$ mmHg for patients 18 years of age and older (Grade E). Evidence from three trials demonstrates improved cardiovascular and cerebrovascular health outcomes, as well as reduced mortality in adults with diabetes treated to a SBP goal of < 150 mmHg.^{18–20} In the absence of RCTs of health outcomes in adult patients with diabetes comparing SBP goal < 150 mmHg with < 140 mmHg, the panel recommended a blood pressure goal of $< 140/90$ mmHg in adults with diabetes based on expert opinion.

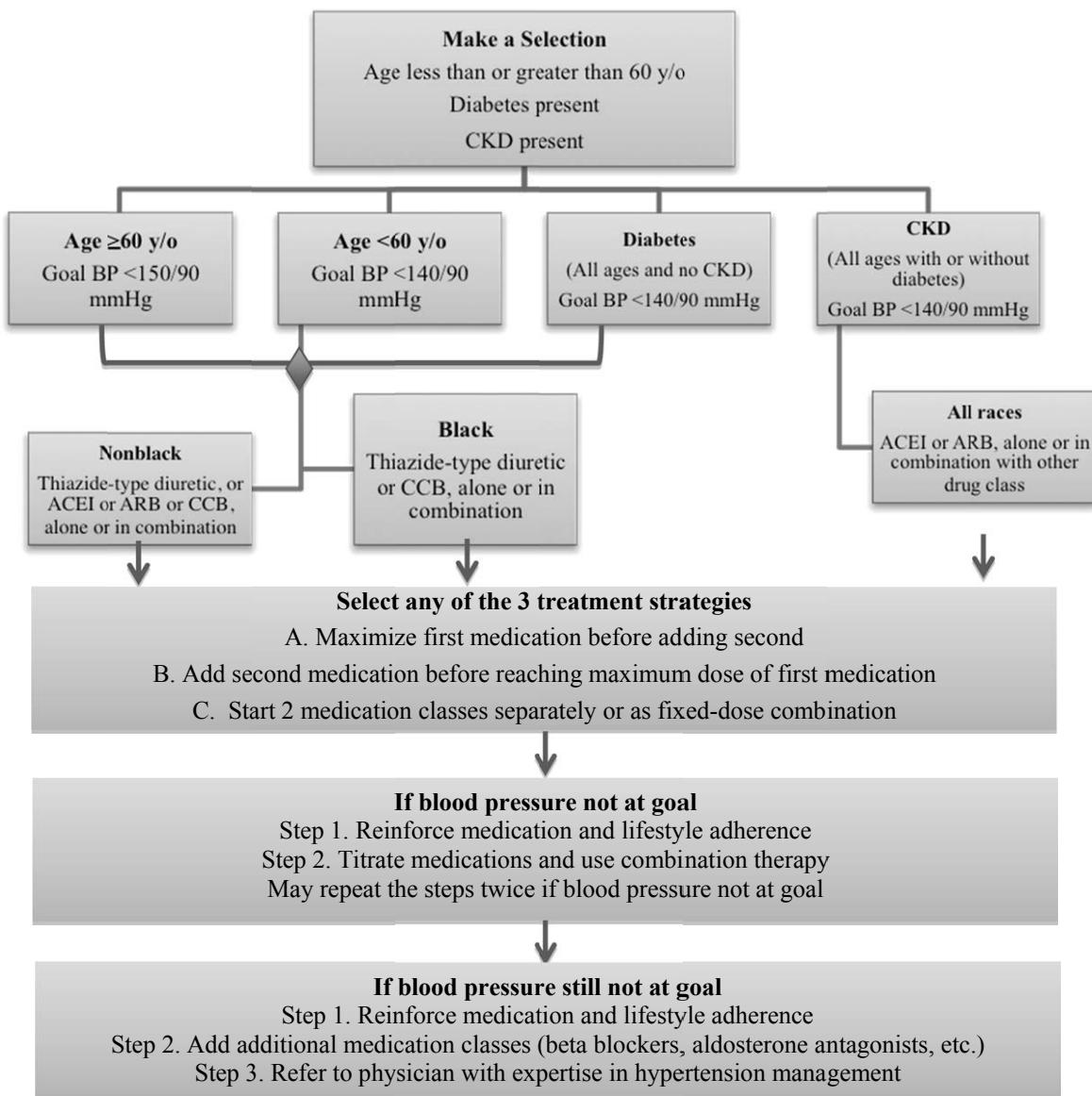
In the general non-black patient population, including diabetics, it is recommended to initiate patients on a thiazide-type diuretic, CCB, ACEI, or ARB (Grade B). In the general black population, including diabetics, initial pharmacologic treatment should include a thiazide-type diuretic or CCB (Grade B for general black population; Grade C for black patients with diabetes). This recommendation is based on a subgroup analysis of the ALLHAT trial in which a thiazide-type diuretic was more effective in reducing cerebrovascular, heart failure, and combined cardiovascular outcomes in the black population compared to an ACEI. CCBs were found to be similar to diuretics for cerebrovascular, cardiovascular, and kidney outcomes and overall mortality and are therefore also included as first-line therapy for hypertension in this patient population.¹⁵

In comparison, the American Diabetes Association Standards of Medical Care in Diabetes recommend patients with diabetes and blood pressure $\geq 140/80$ mmHg should be initiated on pharmacological therapy to achieve SBP goal of < 140 mmHg. It is recommended that the regimen include an ACEI or ARB.²¹

The Pharmacist and New Hypertension Guidelines

JNC8 provides evidence-based recommendations for blood pressure thresholds, blood pressure goals, and treatment strategies. Evidence review based on RCTs resulted in the recommendation of these four drug classes proven to reduce mortality and cardiovascular, cerebrovascular, and kidney outcomes: thiazide-type diuretics; CCBs; ACEIs; and ARBs. Specific recommendations are provided for subpopulations including patients with CKD and diabetes. Guideline recommendations do not take the place of clinical judgment and patient-specific factors; moreover, patient response to treatment should be considered in the therapeutic management of patients with hypertension. Pharmacists play an important role in educating patients about antihypertensive drug therapy and monitoring patient response and adherence.

Figure 1. JNC8 Simplified Management Algorithm



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Continuing Education Quiz: JNC8 Evidence-Based Guidelines for the Management of Hypertension in Adults:
What Pharmacists Need to Know

Pharmacist Post Test	Pharmacy Technician Post Test
1. If left untreated, hypertension can lead to life-threatening complications such as: a. rash, bleeding, headache, and stroke b. stroke, myocardial infarction, heart failure, and cardiac arrhythmias c. renal failure, eczema, blindness, and osteoporosis d. stomach ulcers, seizures, heart failure, and cancer	1. If left untreated, hypertension can lead to life-threatening complications such as: a. rash, bleeding, headache, and stroke b. stroke, myocardial infarction, heart failure, and cardiac arrhythmias c. renal failure, eczema, blindness, and osteoporosis d. stomach ulcers, seizures, heart failure, and cancer
2. JNC8 can be best described as: a. a new drug to treat hypertension that is supported by evidence based medicine b. a list of the top doctors in the U.S. that specialize in cardiology c. a federal organization that collects patient-specific data and outcomes from insurance company databases d. evidence-based recommendations for blood pressure targets and hypertension treatment	2. JNC8 can be best described as: a. a new drug to treat hypertension b. a list of the top doctors in the U.S. that specialize in cardiology c. a federal organization that collects patient-specific data d. recommendations for blood pressure targets and hypertension treatment
3. According to JNC8, for the general population 60 years of age and older, pharmacotherapy should be initiated at a. SBP greater than or equal to 100 or DBP greater than or equal to 90 b. SBP greater than or equal to 150 or DBP greater than or equal to 90 c. SBP greater than or equal to 160 or DBP greater than or equal to 90 d. SBP greater than or equal to 180 or DBP greater than or equal to 90	3. Which statement is true regarding JNC8 guidelines? a. they will be released in 2020 b. they will be released in 2016 c. they have been in effect since 2013 d. they have been in effect since 2002
4. According to JNC8, initial treatment for the general non-black population should include: a. beta blockers, loop diuretics, statins, or ARBs b. alpha1 blockers, thiazides, ACE inhibitors, or beta blockers c. alpha agonists, beta blockers, loop diuretics, or ARBs d. thiazides, calcium channel blockers, ACE inhibitors, or ARBs	4. Medications used to treat hypertension include: a. statins and corticosteroids b. loop diuretics and metformin c. antibiotics and thiazide diuretics d. ACE inhibitors and calcium channel blockers
5. According to JNC8, which statement is true regarding using betablockers for first line therapy to treat hypertension in the general non-black population? a. beta blockers should be first line because they have lower mortality than other agents b. beta blockers should be first line because they have a	5. Which statement is true regarding patients that require medication to treat their hypertension? a. most patients are managed on no medications b. most patients are managed on one medication c. most patients are managed on more than one medication d. most patients should not be on more than two medications

<p>better side effect profile than other agents</p> <p>c. beta blockers should not be used first line because they were found to be inferior to ARBs in preventing CV death, MI, and stroke</p> <p>d. beta blockers should not be used first line because they are more expensive than other agents and are therefore not cost-effective in this patient population</p> <p>6. JNC8 has treatment recommendations for the following patient subpopulations:</p> <ul style="list-style-type: none">a. chronic kidney disease and diabetesb. pregnant women and childrenc. post menopausal women and pregnant womend. diabetes and cancer <p>7. JNC8 blood pressure goals in adult patients with chronic kidney disease are:</p> <ul style="list-style-type: none">a. lower than the goals for patients with diabetesb. higher than the goals for patients with diabetesc. lower than the goals for patients that are over age 60d. higher than the goals for patients that are over age 60 <p>8. According to JNC8, data on treating the general black population comes from the:</p> <ul style="list-style-type: none">a. TIMI8 trialb. ALLHAT trialc. HAVNOT triald. BUNCAT trial <p>9. JNC8 and guidelines in general should:</p> <ul style="list-style-type: none">a. be followed to the letter to prevent malpracticeb. be disregarded in large teaching institutionsc. not replace clinical judgment and patient-specific factorsd. be updated at least annually <p>10. Pharmacists can play an important role in helping to manage hypertensive patients by:</p> <ul style="list-style-type: none">a. educating patients, monitoring patient response, and monitoring patient adherenceb. providing therapeutic substitutions to less costly medication alternativesc. prescribing additional medication therapy to treat common side effects of blood pressure medicationsd. keeping community pharmacies open 24 hours per day to triage hypertensive emergencies	<p>6. JNC8 has more specific recommendations on treating hypertension in patients that:</p> <ul style="list-style-type: none">a. have chronic kidney disease or diabetesb. are pregnant women or are childrenc. are post menopausal women or pregnant womend. have diabetes or cancer <p>7. According to Table 1, JNC8 blood pressure goals in adult patients with chronic kidney disease are:</p> <ul style="list-style-type: none">a. lower than the goals for patients with diabetesb. higher than the goals for patients with diabetesc. lower than the goals for patients that are over age 60d. higher than the goals for patients that are over age 60 <p>8. Information and data that were reviewed in establishing the JNC8 guidelines include:</p> <ul style="list-style-type: none">a. patient surveysb. clinical trialsc. prescription recordsd. insurance databases <p>9. Which statement is true regarding JNC8 and guidelines in general?</p> <ul style="list-style-type: none">a. physicians that follow guidelines pay less malpractice insurance feesb. guidelines are typically followed in smaller communitiesc. a clinician's judgment or patient-specific factors are more important than strict adherence to guidelinesd. guidelines should be updated at least annually <p>10. Pharmacy technicians can play an important role in helping manage hypertensive patients by:</p> <ul style="list-style-type: none">a. monitoring medication refills to see if the patient is adherent to therapyb. recommending cheaper over the counter blood pressure medications to patientsc. prescribing additional medication therapy to treat common side effects of blood pressure medicationsd. keeping community pharmacies open 24 hours per day to triage hypertensive emergencies
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Please circle your answers (one answer per question)

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Passing Score is 70% or above

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Please rate the following items on a scale from 1 (poor) to 4 (excellent).

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| 1. Overall quality of the article | 1 | 2 | 3 | 4 |
| 2. Relevance to pharmacy practice | 1 | 2 | 3 | 4 |
| 3. Value of the content | 1 | 2 | 3 | 4 |

Please answer each question, marking whether you agree or disagree

- | | | |
|---|--------------------------------|-----------------------------------|
| 4. The home study met the stated learning objectives: | <input type="checkbox"/> Agree | <input type="checkbox"/> Disagree |
| 5. The author(s) demonstrated topic mastery | <input type="checkbox"/> Agree | <input type="checkbox"/> Disagree |
| 6. The home study provided a valuable learning experience | <input type="checkbox"/> Agree | <input type="checkbox"/> Disagree |
| 7. My personal objectives in completing the home study were fulfilled | <input type="checkbox"/> Agree | <input type="checkbox"/> Disagree |
| 8. The material was presented in a fair and unbiased manner. It was not commercial in nature. | | |

Agree Disagree

Impact of the Activity

9. The information presented (check all that applies):
- Reinforced my current practice/treatment habits
 - Will improve my practice/patient outcomes
 - Provided new ideas or information I expect to use
 - Adds to my knowledge
10. Will the information presented cause you to make any changes in how you do your job?
- Yes No

11. How committed are you to making these changes? (Not - Very) 1 2 3 4

12. Do you feel future activities on this subject matter are necessary and/or important?
- Yes No

Follow-Up

As part of our ongoing quality-improvement effort, we would like to be able to contact you in the event we conduct a follow-up survey to assess the impact of our educational activities on professional practice. Are you willing to participate in such a survey?

Yes No

JNC8 Evidence-Based Guideline for Management of Hypertension in Adults: What Pharmacists Need to Know

This lesson is a knowledge-based CE activity and is targeted to pharmacists and pharmacy technicians. This program has been approved for 1 contact hour of continuing education credit (0.1 CEU). UAN: 0136-0000-15-019-H01-P; 0136-0000-15-019-H01-T. Release Date: 07/06/2015; Expiration: 07/06/2015

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Advances in the Treatment of Pulmonary Hypertension: Focus on Adempas and Opsumit

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Dr. Thomas A. Gossel has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide information on pulmonary hypertension and its therapy, with emphasis on two recently approved drugs, macitentan (Opsumit[®]) and riociguat (Adempas[®]).

Objectives. At the completion of this activity, the participant will be able to:

1. recognize signs and symptoms, and key features of pulmonary hypertension including information on its prevalence;
2. identify the drugs by generic name, trade name, and chemical name when relevant;
3. recognize the indication(s), pharmacologic action(s), clinical application(s), and route of administration for each drug;
4. demonstrate an understanding of adverse effects and toxicity, warnings, precautions, contraindications, and significant drug-drug interactions; and
5. list important information to convey to patients and/or their caregivers.

Pulmonary hypertension (PH) is a hemodynamic and pathophysiologic condition. Both progressive and debilitating, with a median survival of only 2.8 years following diagnosis if left untreated, PH is defined as mean pulmonary artery pressure (mPAP) of 25 mmHg or greater at rest. The normal mPAP is 12 to 16 mmHg. Patients with PH have a sustained increase in

pulmonary arterial pressure that results from excessive vasoconstriction of the pulmonary arteries. The workload of the heart's right ventricle is therefore increased, leading to its failure and, eventually, death. Treatment of PH is largely palliative, and disease progression continues despite availability of drugs that are specific for the disorder.

This lesson reviews PH and provides a brief introduction to

the drugs used in its treatment with focus on two newly approved therapies. The lesson is not meant to extend beyond an overview of the topic. The reader is, therefore, urged to consult the products' full Prescribing Information leaflet (package insert), *Medication Guide*, and other published reference sources for detailed descriptions.

Background

The World Health Organiza-

Table 1
WHO categories of pulmonary hypertension

Group 1 pulmonary arterial hypertension includes:

- PAH that has no known cause (idiopathic)
- PAH that is inherited (genetic)
- PAH caused by drugs or toxins, such as street drugs and certain diet medications
- PAH caused by conditions such as connective tissue diseases, HIV infection, liver infection, chronic hemolytic anemia, sickle cell disease, schistosomiasis (one of the most common causes of PAH in many parts of the world)
- PAH caused by conditions that affect the pulmonary vasculature

Group 2 pulmonary hypertension includes:

- PH due to left heart disease. Conditions that affect the left side of the heart, such as mitral valve disease or long-term hypertension, can cause left heart disease and PH. Left heart disease is likely the most common cause of PH.

Group 3 pulmonary hypertension includes:

- PH associated with lung disease and/or hypoxia, such as COPD* and interstitial lung diseases. Interstitial lung diseases cause scarring of lung tissue. Group 3 also includes PH associated with sleep-disordered breathing, chronic exposure to high altitude, and developmental abnormalities.

Group 4 pulmonary hypertension includes:

- PH caused by chronic thromboembolic disease characterized by obstruction of the pulmonary vasculature by residual organized thrombi, leading to increased pulmonary vascular resistance, progressive PH, and right ventricular failure

Group 5 pulmonary hypertension includes:

- PH caused by various other diseases or conditions. Examples include blood diseases such as polycythemia vera, thrombocythemia; systemic disorders such as sarcoidosis, vasculitis; and metabolic disorders such as thyroid disease and glycogen storage disease
- PH caused by other conditions such as tumors that press on the pulmonary arteries and kidney disease

*COPD – chronic obstructive pulmonary disease

Table 2
WHO functional classification for patients with pulmonary hypertension

Class	Description
I	Patients with PH but without resulting limitations of physical activity; ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
II	Patients with PH resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
III	Patients with PH resulting in marked limitation of physical activity; they are comfortable at rest; less-than-ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
IV	Patients with PH with an inability to carry out any physical activity without symptoms; these patients manifest signs of right heart failure; dyspnea and/or fatigue can even be present at rest; discomfort is increased by any physical activity

tion (WHO) recognizes a number of etiologies that cause PH and divides them into five categories of disease (Table 1). These groups are organized based on the cause of PH and treatment options. Note that Group 1 is referred to as pulmonary arterial hypertension (PAH) and Groups 2 through 5 are called pulmonary hypertension. However, together, all Groups are collectively called *pulmonary hypertension*.

In addition to the etiological classification of PH, patients can also be classified according to their functional abilities and symptom severity (Table 2). The WHO classification of functional capacity is modeled after the New York Heart Association's classification system for heart failure and is commonly used in both daily practice and clinical trials to describe patients. The WHO functional class is determined from the patient's own

subjective impression of physical ability and symptom severity. The indications for FDA-approved treatments of PH specify the WHO classification.

The terms "primary" and "secondary" PH are historical and even though they are still mentioned informally in association with the various forms of the disease, their use is now discouraged. The terms suggest clinically inappropriate groupings of the disorders and may thus promote inadequate therapeutic decision making.

Pathogenesis. Left heart disease is the most common cause of PH. There is, however, a relative lack of data on the frequency of pathologic pulmonary vascular changes in this heterogeneous group of patients. WHO Group 1 PAH is predominantly a disease of the distal pulmonary arteries (i.e., pulmonary artery vasculopathy). Associated pathology includes pulmonary arterial vasoconstriction, medial hypertrophy, intimal proliferation and fibrosis, complex plexiform lesions, and thrombotic lesions. Pathologic changes in PAH typically onset as a compensated phase characterized by abnormal pulmonary artery endothelium, pulmonary arterial vasoconstriction and stiffening, loss of microvessels, and right ventricle hypertrophy. As PAH progresses, pulmonary vascular intimal proliferation, obliterative pulmonary artery remodeling, and pulmonary vascular fibrosis occur and eventually progress to right ventricle dilation and failure.

Symptoms. Progressive dyspnea is the most common symptom of PH, being the initial symptom in greater than half of patients with PH. It ultimately appears in approximately 85 percent of patients. Since exertional dyspnea is a common symptom of multiple cardiopulmonary pathologies, and PH is relatively uncommon with many primary care physicians never encountering a case, clinicians need a high index of suspicion to correctly identify patients with the condition, especially those

who present at a younger age and patients diagnosed with concurrent asthma. Even as awareness of the disease has increased over the past two decades, delay from symptom onset to diagnosis is still considerable, with 20 percent of patients experiencing symptoms for longer than two years before a diagnosis of PH is made and treatment is initiated.

Other symptoms include fatigue (26 percent), chest pain (22 percent), lower-extremity edema (20 percent), presyncope/syncope (17 percent), and palpitations (12 percent). As PH worsens, patients may find it difficult to undertake any physical activity. A rare symptom known as the Ortner syndrome is characterized by onset of hoarseness from compression of the left laryngeal nerve by an enlarged pulmonary artery.

Prognosis. PH is considered a negative prognostic sign in many pathologic conditions, including the most commonly associated ones, such as heart failure and chronic obstructive pulmonary disease (COPD). For heart failure, elevated pulmonary arterial pressure on right heart catheterization is a powerful predictor of premature mortality, particularly in the setting of myocarditis or decreased right ventricular ejection fraction. Likewise, patients with COPD and more severe PH have a poorer prognosis. Treatment directed at PH has not been linked to improved outcomes in either of these pathologic conditions.

As noted earlier, the prognosis of untreated PH is poor, with a median survival of 2.8 years, and an estimated one-year survival of only 68 percent. Treatment with approved therapies has improved survival and quality of life, if initiated early in the course of the disease. But PH continues to be a life threatening condition.

Treatment of Pulmonary Hypertension

Appropriate treatment for PH relies on identification of its cause. For persons with chronic cardiac

Table 3
Advanced therapies for pulmonary hypertension

Drug Class	Mechanism of Action
<i>Prostacyclin analogues</i>	Stimulates intracellular production of cAMP [‡]
Epoprostenol (Flolan, Veletri)	
Iloprost (Ventavis)	
Treprostinil (Remodulin, Tyvaso)	
<i>Endothelin-receptor antagonists</i>	Blocks endothelin-1 receptors on vascular smooth muscle
Ambrisentan (Letairis)	
Bosentan (Tracleer)	
<i>Phosphodiesterase-5 inhibitors</i>	Inhibits breakdown of cGMP [§] in vascular smooth muscle
Sildenafil (Revatio, Viagra*)	
Tadalafil (Adcirca, Cialis*)	

[‡]cAMP – cyclic adenosine monophosphate
[§]cGMP – cyclic guanosine monophosphate
* Cialis and Viagra are not indicated for treatment of PH

or pulmonary disease, therapy is largely focused on treating the underlying condition.

To date, the majority of drug development in PH has been focused on patients with WHO Group 1 PAH. Approved therapies fall into one of three classes of pulmonary vasodilators: (1) prostacyclin analogues, (2) endothelin receptor antagonists (ERAs), and (3) phosphodiesterase-5 inhibitors. These are collectively termed “advanced therapies” (Table 3), and are available for oral, inhaled, subcutaneous, and intravenous administration. Each therapy targets a different cellular pathway implicated in the pathogenesis of PAH.

Prostacyclin Analogues.

Prostacyclin is also referred to as prostaglandin I₂ (PGI₂). Prostacyclins were the first available targeted treatment for PAH and are at present considered the cornerstone of therapy. They have potent vasodilatory, antiplatelet, and antiproliferative properties on the pulmonary vasculature and their synthesis is reduced in patients with PAH. Synthetic prostacyclin derivatives augment decreased prostacyclin levels.

Endothelin Receptor Antagonists. Endothelin is a potent vasoconstrictor and stimulator of smooth muscle cell proliferation. It contributes to the regulation of

vascular tone by binding to ET_A and ET_B receptor subtypes in the pulmonary vasculature. Activation of ET_A receptors results in vasoconstriction and cellular proliferation. Pharmacotherapeutic influence in these reactions, therefore, is a primary target of ERAs. ET_B is thought to have a regulatory effect on endothelin; however, the clinical relevance of blocking this receptor is unknown. Endothelin may be overexpressed in patients with PAH and, hence, is an important drug target.

Risks related to treatment with ERAs are well known, and include elevations in liver aminotransferases and edema. Their effect on the liver is possibly a class effect and necessitates monitoring of liver function in patients treated with these compounds. The voluntary withdrawal from the world market of the ERA, sitaxsentan, with cessation of all ongoing clinical trials because of cases of unpredictable serious liver injury, illustrates the need for new compounds that have reduced hepatic liability. The drug was never approved in the United States.

Similarly, a reduced risk of edema would constitute a major advance and would allow for the application of ERAs in other diseases. This is demonstrated by recent findings with the experimental

ERA, darusentan, in patients with treatment-resistant hypertension. While darusentan provided additional reduction in blood pressure in patients in whom hypertension could not be controlled adequately with available drugs, edema occurred in 27 percent of patients compared with 14 percent in patients treated with placebo. The drug’s future for approval in the United States remains in question at present.

The mechanism by which ERAs induce liver aminotransferases is unknown. It has been hypothesized that inhibition of the bile salt export pump, a transporter protein involved in mediating secretion of bile salts across the canalicular plasma membrane of hepatocytes, results in intracellular accumulation of bile salts with subsequent hepatic injury. The occurrence of edema is possibly caused by circulating endothelin-1 via activation of the ET_B receptor, suggesting that ERAs that block both ET_A and ET_B receptors are less prone to causing edema.

Phosphodiesterase Type-5 Inhibitors.

Phosphodiesterase type-5 (PDE-5) inhibitors work via the nitric oxide (NO) pathway. They are responsible for the degradation of cyclic guanosine monophosphate (cGMP), which plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis, and inflammation. PH is associated with impaired NO release and reduction of cGMP concentration in the pulmonary tissue. PDE-5s increase cGMP concentration resulting in relaxation of the smooth muscle cells leading to vasodilation of the pulmonary vessels. Intracellular cGMP plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis, and inflammation. PH is associated with endothelial dysfunction, impaired synthesis of NO, and insufficient stimulation of the NO-sGC-cGMP pathway.

Combination Therapy. The current status of PH treatment is based on sequential addition of

advanced therapies. Therapy is chosen initially by assessing illness severity and patient functional class, along with integrating patient preferences and adverse effect profiles of the medications being considered. If PH worsens despite optimum dosing of a single agent, additional therapies from different pharmacologic groups are usually added until treatment goals are reached.

Extending Survival and Quality of Life

A significant number of patients with PH experience little or no improvement despite available therapies, and mortality remains high despite treatment. There is, therefore, an unmet need for drugs that extend survival and improve quality of life in PH patients, while also having a favorable safety profile and a convenient mode of administration.

New drugs with novel mechanisms of action are at various levels of development. At present, clinicians are challenged not by having too few therapeutic options, but by having to choose among the various treatments available, monitoring patients for stability, and recognizing when to escalate pharmacotherapy or consider surgical options (lung transplantation or atrial septostomy). Atrial septostomy is a surgical procedure in which a small hole is created between the heart's two atria. This relieves some of the pressure within the pulmonary vasculature, but at the expense of reduced oxygen levels in the heart (hypoxia).

Goals of Therapy. The goals of therapy are to prevent advancement of the disease; decrease hospital admissions; and improve quality of life (decreased symptoms), WHO functional class (increased activity levels), hemodynamics, 6-minute walk results, and overall survival. Specific PH therapy is usually started for symptomatic patients in WHO functional classes II, III, or IV if they fail to show no acute vasoreactivity or if they did not maintain an acceptable sus-

tained response to calcium channel blockers. General supportive measures are listed in Table 4.

Recently Approved Drugs

Two new drugs for PH were approved in October 2013 (Table 5). The two drugs differ in their basic pharmacology, but both share one troublesome toxicologic effect – they both may cause fetal harm when administered to pregnant females.

Because of this potential toxicity, female patients can receive the new drugs only through the manufacturers' Risk Evaluation and Mitigation Strategy (REMS) program. All female patients must be enrolled in the program, comply with pregnancy testing requirements and be counseled regarding the need for effective contraception. The REMS restricted distribution program requires prescribers to be certified by enrolling in the program. Also, pharmacies must be certified and can dispense the new drugs only to patients who are eligible to receive it. Males need not be enrolled in the program.

Riociguat (Adempas)

Indications and Use. Adempas (a-dem-pahs) was the first drug of any class to be shown to be effective for patients with chronic thromboembolic PH (CTEPH). It is indicated for treatment of adults with persistent/recurrent CTEPH (WHO Group 4) following surgical treatment or inoperable CTEPH, to improve exercise capacity and WHO functional class. It is also indicated to treat PAH (WHO Group 1), to improve exercise capacity, improve WHO functional class, and to delay clinical worsening.

Mechanism of Action. Riociguat has a dual mode of action. It sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding. The drug also directly stimulates sGC via a different binding site, independently of NO. The drug stimulates the NO-sGC-cGMP pathway and leads to increased generation of cGMP with subsequent vasodilation. The active metabolite of

Table 4
General supportive measures for patients with pulmonary hypertension

General recommendations

- Symptom-limited exercise
- Avoid hypobaric environments, including high-altitude travel
- Avoid medications with vasoconstrictive properties (e.g., pseudoephedrine)
- Discourage pregnancy due to high maternal mortality
- Avoid oral contraceptives with prothrombotic properties

Medical therapy

- Anticoagulation to a target INR of 1.5 to 2.5; recommended for most patients
- Oxygen supplementation for hypoxemia
- Diuretics for management of edema or fluid retention, especially in the setting of right ventricular failure
- Consider digoxin, particularly for patients with a high sympathetic activation or with concomitant atrial fibrillation or biventricular failure
- Long-term calcium channel blockers for patients who have a genuine acute vasoreactivity test and calcium channel blocker challenge without significant side effect, (fewer than 7 percent of patients are in this subgroup)

riociguat is 1/3 to 1/10 as potent as the parent drug *in vitro*.

Efficacy and Safety. Safety and effectiveness of Adempas to treat CTEPH were established in a clinical trial with 261 participants randomized to take Adempas with the dose gradually increased up to 2.5 mg three times daily, or to receive a placebo three times daily. The study was designed to measure the change in distance a patient could walk in six minutes. After 16 weeks of treatment, the average improvement in a six-minute walk distance in participants treated with Adempas was 46 meters (about 150 feet) more than in those treated with placebo.

The clinical trial evaluating the safety and effectiveness of Adempas to treat PAH included 443 participants randomly assigned to

Table 5
New drugs for treatment of pulmonary hypertension

Generic Name	Distributor	Indication	Dose	Dosage Form	Medication Guide
Macitentan (Opsumit)	Actelion Pharmaceuticals US, Inc.	PAH* (WHO Group 1)	10 mg once daily	10 mg tablets	Yes
Riociguat (Adempas)	Bayer Health-Care Pharmaceuticals Inc.	PAH* (WHO Group 1); CTEPH [‡] (WHO Group 4)	1 mg three times daily (range: 0.5 mg to 2.5 mg three times daily)	0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg	Yes

*PAH – Pulmonary Arterial Hypertension

[‡]CTEPH – Chronic Thromboembolic Pulmonary Hypertension

take the drug at a dose of 1.5 mg or 2.5 mg, or placebo, three times daily. After 12 weeks of treatment, the 6-minute walk distance in patients treated with Adempas improved by an average of 36 meters (about 118 feet) more than in patients treated with placebo.

Common adverse effects observed in patients treated with Adempas included headache, dizziness, indigestion, tissue swelling, nausea, diarrhea, and vomiting.

Warnings, Precautions and Contraindications. The following warnings and precautions are listed.

- Symptomatic hypotension:** Adempas reduces blood pressure. Consider dose reductions if the patient develops signs or symptoms of hypotension.

- Bleeding:** Serious hemorrhagic events can occur. Monitor patient for signs and symptoms.

- Pulmonary edema in patients with pulmonary veno-occlusive disease:** Discontinue treatment if confirmed.

- A boxed warning advises that the drug should not be used during pregnancy, and that the drug is available only through a restricted distribution program.**

Three contraindications are listed: pregnancy, use with nitrates or NO donors in any form (e.g., amyl nitrite), and use with phosphodiesterase inhibitors (e.g.,

dipyridamole, theophylline, sildenafil, tadalafil, vardenafil).

Drug Interactions. Noted specifically are strong CYP and P-glycoprotein/breast cancer resistance protein (P-gp/BCRP) inhibitors. For patients receiving strong CYP and P-gp/BCRP inhibitors (e.g., ketoconazole, itraconazole, ritonavir), consider a starting dose of 0.5 mg three times a day. Monitor for hypotension. Antacids such as aluminum- or magnesium hydroxide decrease riociguat absorption, so doses of antacids and riociguat should be separated by at least one hour.

Administration, Dosing, and Counseling. Initiate treatment at 1 mg three times a day. For patients who may not tolerate the hypotensive effect, consider a starting dose of 0.5 mg three times a day. Dosage may be increased by 0.5 mg intervals of no sooner than two weeks as tolerated, to a maximum dose of 2.5 mg three times a day. If a dose is missed, continue with the next regularly scheduled dose. In the event that Adempas dosing is interrupted for three or more days, re-titrate the drug.

Plasma concentrations are reduced 50 to 60 percent in smokers. Consider titrating to dosages higher than 2.5 mg three times a day if tolerated in patients who smoke to match exposure seen in non-smokers. A decrease in dosage

Table 6
Patient information for riociguat (Adempas)*

Patients:

- should read the *Medication Guide* carefully and talk with their pharmacist or physician if they have questions.
- (females) should use emergency contraception in the event of unprotected sex or contraceptive failure. Females must sign an enrollment form to register in the Adempas REMS Program; males are not required to do so.
- (pre-pubertal females) should report any changes in her reproductive status immediately to her prescriber.
- should be aware of the potential risks/signs of coughing up blood caused by the drug, and must contact their physician right away if signs/symptoms appear.
- should be aware it is important to stick closely to the dosing, titration, and maintenance of Adempas. If a dose is missed, patients should continue with the next regularly scheduled dose. In event the drug is interrupted for three or more days, the dose should be re-titrated.
- should report all current medicines and new medicines to their physician.
- should not take antacids within one hour of taking Adempas.
- should be aware Adempas can cause dizziness, which can affect the ability to drive and use machines.
- should be aware they should not use Adempas for a condition other than for what it was prescribed, or give it to other people, even if their symptoms are the same.
- should be aware that Adempas should be stored at room temperature between 59°F to 86°F (15°C to 30°C).

*Summarized from the FDA-approved *Medication Guide*

may be required in patients who stop smoking.

Adempas is available in tablets containing 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg of riociguat. Specific points for counseling are summarized in Table 6.

Macitentan (Opsumit)

Opsumit (OP-sum-it) is the second new drug approved during October, 2013 for treatment of PH.

Table 7
Patient information for macitentan (Opsumit)*

Patients:

- should read the *Medication Guide* carefully and talk with their pharmacist or physician if they have questions.
- (females) may experience fetal harm when Opsumit is used during pregnancy. Instruct females to use effective contraception and to contact her physician if she suspects she may be pregnant. Females must sign an enrollment form to register in the Opsumit REMS Program; males are not required to do so.
- (pre-pubertal females) should report any changes in her reproductive status immediately to her prescriber.
- should get hemoglobin levels tested as the physician recommends.
- should be aware the drug may interfere with spermatogenesis.
- should be aware of signs of hepatotoxicity, and contact their doctor if they have unexplained nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching.
- should not split, crush, or chew Opsumit tablets.
- should store Opsumit tablets at 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F)

*Summarized from the FDA-approved *Medication Guide*.

Indications and Use. The new drug is an ERA indicated for treatment of PAH (WHO Group 1) to delay disease progression. During clinical trials, disease progression included: death, initiation of intravenous or subcutaneous prostanoids, or clinical worsening of PAH (decreased six-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). The new drug also reduced hospitalizations for PAH.

Mechanism of Action. Endothelin (ET)-1 and its receptors (ET_A and ET_B) mediate a variety of deleterious effects, such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. In

disease conditions such as PAH, the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage. Macitentan is an ERA with high lipophilicity that prevents the binding of ET-1 to both ET_A and ET_B receptors. The dual ERA was developed by modifying the structure of bosentan (Tracleer) to increase efficacy and safety. The new drug is characterized by sustained receptor binding and enhanced tissue penetration. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. One of the metabolites of macitentan is also pharmacologically active at the ET receptors and is estimated to be about 20 percent as potent as the parent drug *in vitro*.

Efficacy and Safety. Safety and effectiveness were established primarily in one long-term clinical trial where 742 participants were randomly assigned to take Opsumit or placebo. The average treatment duration was about two years. In the study, Opsumit was effective in delaying disease progression, which includes a decline in exercise ability, worsening symptoms of PAH, or need for additional PAH medication.

Common side effects observed in persons treated with Opsumit included low red blood cell count, common cold-like symptoms (nasopharyngitis), sore throat, bronchitis, headache, flu and urinary tract infection.

Warnings, Precautions and Contraindications. The following **warnings** and **precautions** are listed.

- *Other ERAs cause hepatotoxicity and liver failure.* Obtain baseline liver enzyme levels and monitor as clinically indicated.

- *Decreases in hemoglobin:* Decreases in hemoglobin concentration and hematocrit have been reported. Measure the hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

- *Pulmonary edema in patients with pulmonary veno-occlusive*

disease: If confirmed, discontinue treatment.

- *Decreased sperm count:* Other ERAs have caused adverse effects on spermatogenesis.

- *A boxed warning advises that the drug should not be used during pregnancy, and that the drug is available only through the Opsumit REMS Program.*

The sole **contraindication** listed is pregnancy.

Drug Interactions. Strong inducers of CYP3A4 (e.g., rifampin) significantly reduce macitentan exposure, thus concomitant use should be avoided. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole) approximately doubles macitentan exposure. Many HIV drugs such as ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of Opsumit with strong CYP3A4 inhibitors.

Administration, Dosing, and Counseling. The recommended dosage is 10 mg once daily orally. Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended.

Opsumit tablets contain 10 mg of macitentan. Specific points for counseling are summarized in Table 7.

Patient Education

In general, patients should be counseled that PH is a complex disease and markedly different than systemic hypertension. Regardless of its cause, serious PH almost always indicates significant systemic disease that requires ongoing, closely coordinated medical care, and close attention to salt intake, fluid balance, and home weight monitoring. Patients with PH may need to self-administer medications that have complex instructions, self-monitor for adverse effects or progression of disease, and help ensure that concomitant health care issues do not compromise or adversely interact with their PH regimen. Patients should also be informed of available information and peer support opportunities. Of tremendous assistance to both

patients and pharmacists is information provided by the Pulmonary Hypertension Association (www.phassociation.org). This site also includes advice for newly diagnosed patients.

Overview and Summary

PH is a relatively rare disease even though its etiological considerations are common. The disease is caused by a variety of etiologies characterized by pulmonary vasculopathy with endothelial

dysfunction, cellular proliferation, and elevated pulmonary vascular resistance. Over the previous two decades there have been profound advancements in PH targeted treatments, resulting in symptom improvement, slowed disease progression, and improved survival. Two recently approved drugs have been added to the treatment armamentarium. Overall, further advancements are needed to prolong life expectancy and improve quality of life in these patients.

The author, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.

This lesson is a knowledge-based CE activity and is targeted to pharmacists in all practice settings.

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continuing education quiz

Advances in the Treatment of Pulmonary Hypertension: Focus on Adempas and Opsumit

- Median survival time following diagnosis in persons with untreated pulmonary hypertension is:
 - 1.5 years.
 - 2.0 years.
 - 2.8 years.
 - 3.2 years.
 - The World Health Organization (WHO) recognizes how many categories of pulmonary hypertension?
 - 1
 - 3
 - 5
 - 7
 - The majority of drug development in pulmonary hypertension has been focused on patients in which of the following WHO groups?
 - 1
 - 3
 - 5
 - 7
 - Prostacyclin is also known as prostaglandin:
 - E₁.
 - E₂.
 - I₁.
 - I₂.
 - A drug from the pharmacologic class of compounds considered to be the cornerstone of therapy for pulmonary hypertension is:
 - bosentan.
 - epoprostenol.
 - tadalafil.
 - ambrisentan.
 - Which of the following drugs is responsible for the degradation of cyclic guanosine monophosphate (cGMP) in treating pulmonary hypertension?
 - Ventavis
 - Remodulin
 - Tracleer
 - Revatio
 - All of the following are goals of therapy in treating pulmonary hypertension EXCEPT to:
 - prevent advancement of the disease.
 - decrease activity levels.
 - improve quality of life.
 - decrease hospital admissions.

Completely fill in the lettered box corresponding to your answer.

- | | | |
|--------------------|---------------------|---------------------|
| 1. [a] [b] [c] [d] | 6. [a] [b] [c] [d] | 11. [a] [b] [c] [d] |
| 2. [a] [b] [c] [d] | 7. [a] [b] [c] [d] | 12. [a] [b] [c] [d] |
| 3. [a] [b] [c] [d] | 8. [a] [b] [c] [d] | 13. [a] [b] [c] [d] |
| 4. [a] [b] [c] [d] | 9. [a] [b] [c] [d] | 14. [a] [b] [c] [d] |
| 5. [a] [b] [c] [d] | 10. [a] [b] [c] [d] | 15. [a] [b] [c] [d] |

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8. The product approved for treating patients with chronic thromboembolic pulmonary hypertension is:

 - Adempas.
 - Adcirca.
 - Opsumit.
 - Floлан.

9. All of the following are contraindications to use of riociguat EXCEPT:

 - pregnancy.
 - decreased hemoglobin.
 - use with nitrates.
 - use with phosphodiesterase inhibitors.

10. Patients taking Adempas should be advised to avoid taking which of the following drugs within one hour of Adempas?

a. Decongestants	c. Antihistamines
b. Cathartics	d. Antacids

11. Plasma concentrations of riociguat may be reduced by how much in smokers?

a. 20 to 30 percent	c. 40 to 50 percent
b. 30 to 40 percent	d. 50 to 60 percent

12. Opsumit is classified as a/an:

 - endothelin receptor antagonist.
 - prostacyclin derivative.
 - phosphodiesterase-5 inhibitor.
 - janus kinase inhibitor.

13. Macitentan was developed by modifying the chemical structure of:

a. bosentan.	c. treprostinil.
b. ambrisentan.	d. tadalafil.

14. All of the following are precautions/warnings for use of macitentan EXCEPT:

a. decreased hemoglobin.	c. symptomatic hypotension.
b. pulmonary edema.	d. decreased sperm count.

15. Advice for persons taking Opsumit includes:

 - avoid driving or operating heavy machinery.
 - keep unopened bottles of Opsumit refrigerated.
 - do not crush or chew tablets.
 - avoid sunlight or exposure to UV bulbs.

To receive CE credit, your quiz must be received no later than April 15, 2017. A passing grade of 80% must be attained. CE credit for successfully completed quizzes will be uploaded to the CPE Monitor. CE statements of credit will not be mailed, but can be printed from the CPE Monitor website. Send inquiries to opa@ohiopharmacists.org.



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Practice Spotlight:

Mahatma Ghandi said it best: "The best way to find yourself is to lose yourself in the service of others." Preparation started months in advance. The research of supplies and organization of medications needed to stock our makeshift, traveling pharmacy had begun. Vaccinations schedules, visas and the thought of all the possible things that could go wrong on this trip circulated in my thoughts. Mosquito nets, bug spray, anti nausea medications, antibiotics, anti-malaria medications filled my supply bag for this trip to an isolated part of Africa, namely Kenya. Everyday, I'd check off long lists in preparation for Kenya, and all during the very beginning of the ebola outbreak.

Kenya is a vast and beautiful place. Safari, beaches, booming tourism. But I wasn't going to Mombasa to enjoy the crystal clear water of the Indian ocean or a luxurious hammock in a lush, green safari park. No, we landed in Ethiopia, flew to Nairobi then to Kitale to journey west toward the outskirt villages and travel some more toward the western border at which point Mt. Elgon overpowers the landscape and separates the Kenyan Ugandan border. We travelled to remote villages that no one would ever venture into unless there was a need to. The need was apparent.

We travelled by bus during the Kenyan rainy season up and down muddy, sloping hills for hours to reach each secluded village. At times, the roads were so saturated, the red earth could not support the weight of the bus loaded with staff and supplies that we would disembark and walk behind the bus up the hills. As we drove, we'd pass cornfields speckled with tiny huts with chickens in the yards. At times, we'd pass sunflower fields with barefoot women balancing jars on their heads and wearing colorful violet, yellow or orange dresses as they'd walk along the road. Often, on these bumpy roads we'd see men masterfully riding old bicycles,



loaded to capacity with supplies. At moments, we would have to stop and respect the cow herder and his flock of brown and white cows as they crossed the path.

This place was vast. It was humbling as you realize just how small we are as humans when you look across the Great Rift Valley; a never-ending sea of land that can't be visually digested all in one view.

As we reached our destination, we would hear children singing, smiling and waving at us as they ran alongside the bus as we pulled into the gates of their village. It was a joyous moment for them to see the American healthcare providers arrive. Unlike for you and I, these villages don't have accessibility to doctors, hospitals or pharmacies. They still live under

an Elder Hierarchy even though their government is becoming more democratic. We would see the school children line up in their uniforms to greet us and they would wave and jump and hug us as we stepped off the bus.

The lucky children wore the uniforms. Every clinic day we could distinguish the health of the village based on the health of the children. The lucky children were able to attend school and get a meal and perhaps have shoes. The unlucky children did not wear shoes and they would

line up for clinic with most likely more infection than their peers.

Clinic was made up of fifty clinicians, medical non medical staff and students and was broken up into a train car style clinic. Patients would line up at the gates and be escorted to registration, triage, well clinic or sick clinic, education, pediatric clinic, dermatology, acupuncture, dentist and finally pharmacy. The team consisted of Doctors, Pharmacists, Physician Assistants, Nurse Practitioners, Nurses, students and non-medical personnel. As

they made their way down the clinics, they would end at the pharmacy where myself and my team would prepare, dispense and most importantly educated each and every patient on their medication. With the help of our translators, we ensured that every patient received the counseling necessary.

The role of the pharmacist on these medical missions is crucial. Most of the patients seen in clinic are poor and uneducated. We were caring for acute illness and allergy, infection, malaria, vitamin A deficiency, parasitic infection, dermatologic conditions, venereal infections, pain and indigestion were rampant amongst these patients. These patients at times were seeing medication for the first time. Education down to the use of a blister pack foil and the need to remove the tablet from it was a necessity. There were no stupid questions in this pharmacy. Every patient took their medication in front of the pharmacist and translator and it was confirmed that they were able to echo back the directions for use of their medications. Patients in pharmacy were so grateful and thought of us a miracle workers and magicians with the magic pills. We would wait for the brown well water to arrive and paper cups of water would accompany each ziplock baggie filled with medication for each patient.

We arrived during the Kenyan rainy season. Our mornings would start cloudy, the day would be sunny and at 5 o'clock the clouds would open each evening. Rain or shine, in ponchos and wet

shoes we made sure each and every patient was counseled and properly dosed. The clinics were busy and bustling and pharmacy runners would run batches of medications directly to teams. Pharmacists on these medical missions were never commonplace. The team leader would constantly remind the team that we have not one but two clinical pharmacists on staff. When we first landed in Kenya, the team thought we were just two women there to help and by the end of the trip, we were given a standing ovation, especially the dermatology department who worked hand in hand with pharmacy. The emergency room physician assistant of the trip made the best comment. He told the medical students "If you don't know something, just go to the pharmacists because they know everything!" Thank you International Medical Relief for allowing us to make pharmacists proud and show what a vital part of the healthcare team we represent.

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Edoxaban: A New Factor Xa Inhibitor

by Janine S. Douglas, Pharm.D., BCPS * & Trevor T. Riley, Pharm.D., BCPS

Introduction

Atrial fibrillation (AF) is a type of cardiac arrhythmia affecting 3 to 6 million Americans and its prevalence is expected to continue to reach 12 million by 2050.^{1,2} Patients with AF may have long-term complications including increased risk of thromboembolic stroke and recurrence of arrhythmias, which result in significant mortality and morbidity.³ For many decades, warfarin, a vitamin K antagonist, was the only oral anticoagulant available for use in the prevention of ischemic stroke and systemic embolism in nonvalvular atrial fibrillation (NVAF).

The use of warfarin in NVAF management has many limitations such as a narrow therapeutic index, numerous drug-drug interactions, food-drug interactions, regular blood monitoring and frequent dose adjustments. Therefore, the development of target specific oral anticoagulants (TSOAC) provides alternative oral options with rapid onsets of action, more predictable pharmacokinetics, with fewer drug-drug interactions, as well as less dose adjustments.³

Since 2010, the United States Food and Drug Administration (FDA) has approved three TSOACs, dabigatran, rivaroxaban, and apixaban, for the prevention of stroke and systemic embolism in patients with NVAF and treatment of venous thromboembolism.^{5,6,7} In clinical trials, all three TSOACs have demonstrated noninferiority to warfarin for the prevention of stroke and systemic embolism and associated with less risk of intracranial bleeding.^{8,9,10} Current guidelines recommend the use of either dabigatran, rivaroxaban, apixaban or warfarin in patients with NVAF with prior stroke, transient ischemic attack (TIA), or CHA₂DS₂-VASc score of 2 or greater.⁴

In addition to the prevention of stroke and systemic embolism, all TSOACs are indicated for the treatment of venous thromboembolism (VTE) defined as deep vein thrombosis (DVT) or pulmonary embolism (PE).^{5,6,7} During the acute phase of VTE management, the standard of care is parenteral anticoagulation with unfractionated heparin, low molecular weight heparin, or fondaparinux followed by warfarin or a TSOAC.³ Rivaroxaban is the only TSOAC indicated for the treatment of VTE without prior parenteral anti-coagulation therapy.⁶

Edoxaban (Savaysa®) was approved by the FDA in January 2015 for the prevention of stroke and systemic embolism in patients with NVAF and the treatment of VTE.¹¹ For the prevention of stroke and systemic embolism in patients with NVAF, the recommended dose is 60 mg once daily without regard to meals. In patients with CrCl ≤ 15-50 ml/min, the dose should be reduced to 30 mg daily. Edoxaban should not be used in patients with CrCl ≥ 95 ml/min for prevention of stroke or systemic embolism in NVAF due to the increased risk of stroke observed in clinical trials.^{11,12} For the treatment of VTE, the recommended dose is 60 mg daily following 5 to 10 days of parenteral anticoagulant therapy. For patients with low body weight (≤ 60 kg), CrCl ≤ 15-50 ml/min,

or using P-glycoprotein inhibitors, the dose should be reduced to 30 mg daily.^{11,13} The goal of this review is to provide an overview of edoxaban, efficacy compared with warfarin, and discuss the potential place in therapy among other TSOACs.

Pharmacology

Edoxaban is a direct factor Xa inhibitor that exhibits concentration dependent inhibition of free factor Xa resulting in decreased generation of thrombin and thrombus formation.^{11,14} At therapeutic doses, changes in PT, INR, and aPTT are expected but are not clinically relevant in monitoring anticoagulant effects of edoxaban.¹¹ Edoxaban has a rapid onset of action and exhibits peak anticoagulant activity within 1-2 hours of oral administration. It is approximately 55% bound to plasma proteins and has a terminal half-life of 10-14 hours. Edoxaban has an absolute bioavailability of 62% and can be administered without regard to meals. Edoxaban undergoes metabolism via hydrolysis into various metabolites. M-4 is the predominant metabolite; however, the large majority of edoxaban is excreted unchanged.¹¹ Edoxaban is approximately 50% renally cleared, while the remainder is cleared by hepatic and biliary mechanisms. In patients with renal impairment, CrCl ≤ 15-50 ml, a 50% dose reduction is recommended to decrease risk of bleeding. The potential for edoxaban accumulation exists due to impaired clearance.¹¹

Adverse effects/ Drug Interactions

Common adverse effects observed in clinical trials include anemia and bleeding.¹² Rates of major bleeding, life threatening, and intracranial bleeding were significantly less compared to warfarin. Gastrointestinal bleeding rates were significantly higher in patients receiving high dose (60 mg) compared to patients receiving low dose edoxaban (30 mg) or warfarin. Other adverse effects include rash, abnormal liver function tests, and interstitial lung disease.¹¹

Compared to warfarin, edoxaban has few drug interactions. Edoxaban is affected by P-glycoprotein inhibitors and inducers. It is recommended to avoid concomitant use of edoxaban with rifampin. A dose reduction by 50% (i.e., 30 mg daily) is recommended for the treatment of PE or DVT when edoxaban is used with P-glycoprotein inhibitors such as verapamil, quinidine, dronedarone, or short term use of azithromycin, clarithromycin, erythromycin, oral itraconazole and oral ketoconazole.^{11,13} Edoxaban should not be co-administered with other anticoagulants, antiplatelets, and thrombolytics as this may increase the risk of bleeding. In clinical trials, edoxaban has been administered in patients also taking low dose aspirin (≤ 100 mg daily), NSAIDs, and thienopyridines which has resulted in clinically relevant bleeding. Patients who require long-term treatment with aspirin or NSAIDs in addition to edoxaban require careful monitoring to prevent significant bleeding events.¹¹

The use of anticoagulants carry the risk of bleeding. In emergent situations, there may be the need for urgent reversal of TSOACs

like edoxaban. Currently, there are no available agents to reverse the anticoagulant effects of edoxaban. Hemodialysis does not appear to significantly contribute to edoxaban clearance. Therefore, hemodialysis is not recommended as a viable method for reversal.⁵

Clinical Efficacy Trials

ENGAGE-AF TIMI 48

The Effective Anticoagulation with Factor Xa Next Generation In Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) was a three group, multicenter, randomized, double-blind, double dummy trial evaluating two once daily dosing regimens of edoxaban compared with warfarin for the prevention of stroke and systemic embolism in patients with atrial fibrillation.¹² Patients were included in the trial if they were ≥ 21 years of age, had documented atrial fibrillation, a score of 2 or greater CHADS₂ risk assessment, and anticoagulation planned for the duration of the trial. Patients were excluded if they suffered a stroke of any kind within 30 days prior to randomization, an estimated creatinine clearance less than 30 ml/min, use of dual antiplatelet therapy, other indications for chronic anticoagulation, and cardiovascular diseases that would preclude use of edoxaban. Patients were randomized to receive edoxaban 60 mg, edoxaban 30 mg, or warfarin dose-adjusted to an INR of 2.0 to 3.0. Patients who may have previously received a vitamin K antagonist underwent randomization after INR was 2.5 or less. The primary efficacy endpoint was time to first stroke (ischemic or hemorrhagic) or systemic embolic event. When comparing the edoxaban 60 mg group to the warfarin group, a stroke or systemic embolic event occurred in 182 patients (1.18 patients per year) and 232 patients (1.5 patients per year) respectively ($p < 0.001$ for non-inferiority). In comparing the annualized rates of stroke, there was a significantly higher rate of hemorrhagic stroke (0.47% for warfarin, 0.26% for edoxaban, $p < 0.001$) but no difference seen with ischemic stroke. From a safety standpoint, the rate of major bleeding events favored the edoxaban group over the warfarin group (2.75% vs 3.43% respectively, $p < 0.001$). Treatment with edoxaban was also associated with significantly lower rates of death from cardiovascular causes regardless of dose, and similar results with all-cause mortality.¹²

Hokusai-VTE

Edoxaban was evaluated as a potential therapeutic treatment option for venous thromboembolism. In a randomized, double-blind, noninferiority study, 8292 patients were randomized to receive either 60 mg edoxaban, 30 mg edoxaban or warfarin dose adjusted to maintain an internationalized ratio (INR) between 2 to 3. Prior to receiving the study interventions, each patient received open-label heparin (enoxaparin or unfractionated) for a median of 7 days. Treatment with edoxaban or warfarin was to be continued for at least 3 months and a maximum of 12 months for all patients. The primary efficacy outcome was the incidence of symptomatic recurrent VTE, defined as a composite of DVT and fatal or non-fatal pulmonary embolism. The principle safety outcome was the incidence of clinically relevant bleeding, which included both major and non-major bleeding. Of the 4118 patients treated with edoxaban, recurrent VTE occurred 3.2% of patients compared with 3.5% of patients in the warfarin group, displaying non-inferiority. Among the 454 patients with PE and evidence of right ventricular dysfunction, recurrent VTE occurred in 15 (3.3%) in the edoxaban group compared to 30 of the 484 patients (6.2%) in

the warfarin group. Among patients receiving warfarin, the time within therapeutic INR range was 63.5%.¹³

When comparing the safety outcome of clinically relevant bleeding, the composite of major and non-major bleeding events occurred in 8.5% of edoxaban treated patients and 10.3% of warfarin treated patients. This safety endpoint was found to be statistically significant for superiority, with 56 patients needing to be treated to prevent one clinically relevant bleeding event. There were no significant differences in major bleeding between groups.¹³

Place in therapy

Edoxaban is the fourth TSOAC approved for use in NVAF and the treatment of VTE as an alternative to warfarin within the last 10 years. While edoxaban has demonstrated efficacy in clinical trials and has lower rates of bleeding compared to warfarin, there are no head to head trials comparing edoxaban with other TSOACs.^{12,13} Edoxaban is not indicated for prophylaxis of DVT after hip and knee replacement surgery like apixaban and rivaroxaban but there are ongoing trials for this indication. Edoxaban requires indication specific dose reductions in patients with renal impairment, low body weight, or concomitant use of P-glycoprotein inducers. The decision to use one TSOAC over another is dependent on patient preference (once versus twice daily), indication, and cost.

Conclusion

Edoxaban is the newest addition to the class of direct factor Xa inhibitors and target specific oral anticoagulants. It is FDA approved for the prevention of stroke and systemic embolism in NVAF and the treatment of VTE. It is dosed once daily and has few drug interactions. Edoxaban is a viable alternative to warfarin in addition to the other TSOACs currently on the market.

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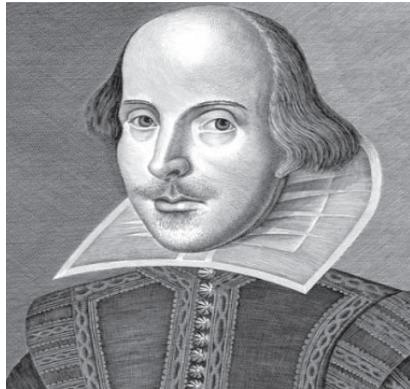
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