Adult Medicine PRN Spring Newsletter

Edited by Ryan Owens, PharmD, BCPS and Lauren McCluggage, PharmD, BCPS

VOLUME 13, ISSUE 1 SPRING 2018

INSIDE THIS ISSUE:

Message from the Chair

Leigh Anne Hylton Gravatt, PharmD, BCPS

Spring has arrived! With spring, it brings new growth, opportunities and a renewed energy for the ACCP Adult Medicine PRN to continue to push ahead developing an environment where pharmacy practitioners can be connected and grow.

Our PRN has continued to capitalize on the momentum we gained over the last two years. In the last two years, our PRN has continued to grow in both numbers but also in engagement. Monthly Journal Club meetings provide a forum for us to connect and discuss the most recent literature that affects our daily practice. Our presence on social media has continued to expand by ensuring our members are aware of the new guidelines and literature that help shape our clinical decisions. This year at the annual meeting we held our first social outing, which was very successful and a great way to connect with other members of our PRN in a relaxed environment. I want to thank the committee members of both the Internal and External Affairs committee for their tireless work engaging and educating our PRN members.

As a PRN, we want to also provide opportunities for our members. This year, with our Research committee leading the charge, we will be setting aside funds to help support the research endeavors of our PRN members. These funds may be used to either support sending a member to the FIT/MERIT program or be used as seed grant funding for a research project. This will be a permanent dedication of funds to better position our PRN members to achieve their research goals and also potentially serve as another way for members to collaborate together on areas of scholarship. I applaud both Rachel Flurie and Rima Mohammed for their work on making this a priority for our PRN.

As always, our PRN is only successful because of the members who give their time and service to this organization. This year alone we had over 90 members who have signed up to volunteer their time to this PRN. I appreciate all of the work that you have all accomplished and I would like to thank the Nominations, Programming, Training and Travel Awards, Internal and External Affairs, Walk-Rounds and the Research Committee leaders and their members. This year we started a new process of making sure that we are providing leadership opportunities to all of our member by rotating the Chairs of each sub-committee and ensuring that we have a succession plan for each of these positions with our vice-chair positions. If you are interested in becoming more involved in the PRN I urge you to think about becoming an Adult Medicine PRN officer or joining one of our committees. Also, if you have thoughts on how we can continue to improve our PRN, please reach out to our executive board and let us know!

Upcoming activities for the PRN include voting for new PRN leadership, applications for the new FIT/MERIT scholarship, as well as Andrew Miesner, Chair-Elect, and his programming committee on developing a great program for the PRN Focus Session, which will be presented at the 2018 ACCP Annual Meeting in Seattle, Washington.

Finally, I want to thank my fellow Adult Medicine PRN officers for their leadership and dedication to this PRN. I want you to know how much I value your contributions and the relationships that I have gained with each of you as well as with our members.

I am looking forward to seeing our PRN continue to grow throughout 2018!

May 4th: PRN Officer Nominations Due

May 23rd - 24th: Virtual Poster Symposium

June 15th; July 15th (Research-In-Progress): Annual Meeting Research Abstracts Due

UPCOMING PRN JOURNAL CLUBS:

MAY 16th

JUNE 20th

FOLLOW US ON SOCIAL MEDIA:

@ACCPAMEDPRN

#AMEDPRN

FACEBOOK.COM/AMEDPRN

2017 Business Meeting Pictures

PRN Clinical Practice Award Winner:
Jennifer Twilla

PRN Student Travel Award Winner: Lauren Moore
PRN Practitioner Award Winner: Jennie Jarrett
PRN Resident Travel Award Winner: Nichole Szczerbowski

PRN Mentoring Award Winner:
Joel Marrs

A Review of the 2018 American Diabetes Association Guideline and Cardiovascular Outcomes Trials

By: Emma M. Gorman, PharmD, BCPS and Casey S. Washington, PharmD, BCPS

"Diabetes is an independent risk for cardiovascular disease in combination with common comorbid conditions with diabetes that are also known to cause ASCVD"

The American Diabetes Association's 2018 Standards of Medical Care in Diabetes were published in the January edition of *Diabetes Care*. A notable change was made in the recommendations for antihyperglycemic therapy for patients with atherosclerotic cardiovascular disease to reflect recent trial data (Table 1). The recommendation was updated for patients with an A1C of at least 9% who require dual antihyperglycemic therapy who also have established atherosclerotic cardiovascular disease. In this patient population it is now recommended to add an agent with the proven ability to reduce major adverse cardiovascular events and/or cardiovascular mortality.[1]

Atherosclerotic cardiovascular disease (ASCVD) is a known macrovascular complication in patients with established diabetes mellitus. It is the leading cause of morbidity and mortality in patients with diabetes and the largest contributor to the direct and indirect cost of diabetes.[2] Diabetes is an independent risk for cardiovascular disease in combination with common comorbid conditions with diabetes that are also known to cause ASCVD. Historically, clinical trials involving antidiabetic agents have focused on glucose control which has been associated with improved microvascular complications, but the effect of antihyperglycemic agents on macrovascular complications has largely remained unelucidated.

Table 1. Pharmacologic treatment approach to Type 2 Diabetes Mellitus

Population	Treatment approach	Recommendations
A1C < 9%	Monotherapy	Metformin
A1C ≥ 9%	Dual Therapy	Metformin + Additional Agent
	ASCVD	Add agent proven to reduce major adverse cardiovascular events and/ or cardiovascular mortality±
	No ASCVD	Add second agent after considera-tion of patient-specific and drug-specific factors
A1C ≥ 10%	Combination Injectable Therapy	Metformin + Basal Insulin

In 2008, the Food and Drug Administration (FDA) issued industry guidance to demonstrate that a new drug therapy will not result in an unacceptable increase in cardiovascular risk prior to approval. The FDA included in their statement a recommendation regarding the cardiovascular outcomes collected, patients included, and trial duration. They recommend that the trial design should assess cardiovascular endpoints and should include, at minimum, a 3 point assessment of Major Adverse Cardiovascular Events (MACE) including cardiovascular mortality, myocardial infarction, and stroke. Additionally, the trial should include patients at higher risk of cardiovascular events including elderly patients, patients with renal impairment, and those with relatively advanced disease. The recommended trial duration to assess the

cardiovascular risk is 2 years. They also state that post-marketing trials will be necessary to demonstrate cardiovascular safety if pre-marketing studies reveal a hazard ratio with an upper 95% confidence interval between 1.3 and 1.8. If the upper limit of the 95% confidence interval hazard ratio is above 1.8, the drug is not approvable under this FDA guidance statement.[3] Some trials utilize a 4 or 5 point MACE assessment which adds hospitalization and/or unstable angina to the outcome, with concern of potentially altering the strength of the outcomes.[4] Results are summarized below in Table 2 and 3.

Table 2. Summary of Cardiovascular Outcomes Trials in Diabetes

Drug (Trial Name)	Population (n)	Inclusion criteria (CVD)	Duration (yrs)	Results [HR (95% CI)]
DPP-4				
Saxagliptin (SAVOR-TIMI 53)[5]	16,492	Age > 40 yrs with CVD **OR** Males > 55 / Females > 65 with at least 1 additional risk factor	2.1	- 3 point MACE: Non-inferior [HR 1.00 (0.89 -1.12)] - Significant increase in hospitalization for HF [HR 1.27 (1.047-1.51)]
Alogliptin (EXAMINE)[6]	5,380	Hospitalization for ACS within 15-90 days	1.5	- 3 point MACE: Non-inferior [HR 0.96 (≤ 1.16)] - Non-significant increase in hospitalization for HF [HR 1.19 (0.90-1.58)]
Sitagliptin (TECOS)[7]	14,671	Age ≥ 50 years with CVD	3	- 4 point MACE: Non-inferior [HR 0.98 (0.88 -1.09)] - No difference in hospitalization for HF [1.00 (0.83-1.20)]
GLP-1				
Lixisenatide (ELIXA)[8]	6,068	Age ≥ 30 yrs with hospitalization for ACS within 15-180 days	2.1	- 4 point MACE: Non-inferior [1.02 (0.89-1.17)]
Liraglutide (LEADER)[9]	9,340	Age ≥50 yrs with CVD **OR** ≥ 60 yrs with at least 1 additional risk factor	3.8	- 3 point MACE: Superior [HR 0.87 (0.78-0.97)] - Significant decrease in all-cause mortality [HR 0.85 (0.74-0.97)] - Significant decrease in CV mortality [0.78
Semaglutide (SUSTAIN-6)[10]	3,297	Age ≥50 yrs with CVD, HF, or CKD 3+ **OR** Age ≥ 60 yrs with subclinical CVD	2.1	- 3 point MACE: Superior [0.74 90.58-0.95)] - Significant decrease in non-fatal stroke [0.61 (0.38-0.99)]
Exendatide (EXSCEL)[11]	14,752	None	3.2	- 3 point MACE: Non-inferior [0.91 (0.83-1.00)]

Table 2. Summary of Cardiovascular Outcomes Trials in Diabetes

Drug (Trial Name)	Population (n)	Inclusion criteria (CVD)	Duration (yrs)	Results [HR (95% CI)]
SGLT-2				
Empagliflozin (EMPA-REG)[12]	7,020	Age ≥18 yrs with CVD	3.1	- 3 point MACE: Superior [0.86 (0.74-0.99)] - Significant decrease in all-cause mortality [0.68 (0.57-0.82)] - Significant decrease in CV mortality [0.62 (0.49-0.77)] - Significant decrease in HF hospitalization [0.65 (0.50-0.85)]
Canagliflozin (CANVAS)[13]	10,142	Age ≥30 yrs with CVD **OR** ≥50 yo with ≥2 risk factors for CVD	2.4	- 3 point MACE: Superior [0.86 (0.75-0.97)] - Non-significant decreased in HF hospitalization [0.67 (0.52-0.87)]

Table 3. Summary of Outcomes

	Superior	Non-Inferior
3 Point MACE	Liraglutide, Semaglutide Canagliflozin Empagliflozin	Saxagliptin Alogliptin Exenatide
4 Point MACE		Lixisenatide Sitagliptin
	Decreased	**No Difference**
All-cause mortality and CV-related mortality	Empagliflozin Liraglutide	Lixisenatide Semaglutide Exenatide Canagliflozin Saxagliptin Alogliptin

	Decreased	No Difference	Increased
Hospitalization for	Empagliflozin Canagliflozin±	Sitagliptin	Saxagliptin Alogliptin±

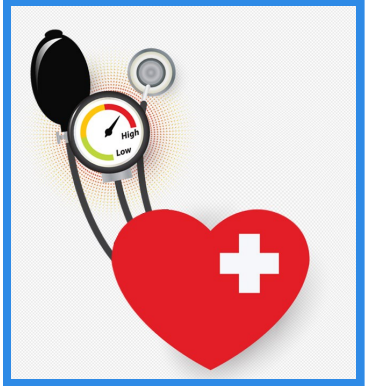
± Non-significant

The FDA has approved the addition of a cardiovascular indication to the package labeling of empagliflozin and liraglutide in response to the outcomes seen in the EMPA-REG and LEADER trials respectively. Empagliflozin was the first to receive the new indication in December 2016 which reads, "to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease."[14] The liraglutide package insert addition was soon to follow in August 2017, adding the indication "to reduce the risk of major cardiovascular events including cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in adult patients with type 2 diabetes mellitus and established cardiovascular disease."[15] There are several on-going cardiovascular outcomes trials poised to be completed in 2018.[16]

Acknowledgements: Article peer-reviewed and edited by Tadd Hellwig, PharmD, BCPS

JNC 8, Already Out of Date: What's Next in Hypertension Management?

By: Alicia M. Hochanadel, PharmD, BCPS and Sarah E. Petite, PharmD, BCPS



"The decision to initiate antihypertensive therapy should be based on patients' 10-year ASCVD risk, as well as BP readings, rather than BP alone"

The latest hypertension guidelines were released in November 2017 by the American College of Cardiology (ACC) and American Heart Association (AHA).[1] The ACC and AHA worked with nine other professional organizations to develop the first comprehensive hypertension guideline review since the Joint National Committee (JNC) 7 guideline release in 2003.[2] In 2014, the JNC 8 guidelines were published; however, new evidence evaluating blood pressure (BP) goals became available following this guideline release.[3] The 2017 ACC/AHA guidelines provide needed comprehensive guidance on hypertension management following the publication of several pivotal studies reexamining BP goals.[1] A review of the 2017 guideline recommendations, as well as key clinical trials, is provided in this article.

BP Classification

The 2017 ACC/AHA guidelines differ from their predecessor, JNC 8, in several key recommendations.[1,3] Table 1 highlights some of those differences. First, the latest guidelines redefine the classification of hypertension, which was last established by JNC 7 in 2003.[2] Blood pressure less than 120/80 mmHg is still considered normal, but lower BP warrants a diagnosis of stage I or II hypertension.[1] Stage I hypertension is now defined as an average systolic blood pressure (SBP) of 130-139 mmHg or an average diastolic blood pressure (DBP) of 80-89 mmHg. Average BP greater than or equal to 140/90 mmHg was previously considered stage I hypertension, now it would be classified as stage II.[1,2] Implementation of the stricter definitions is expected to increase the prevalence of hypertension in the United States from 31.9% to 45.6%.[4] However, the number of patients qualifying for antihypertensive therapy will not increase significantly since a majority of the new patients will require only nonpharmacologic interventions.

Table 1. Recommendations from JNC 8 and the 2017 ACC/AHA Guidelines[1,3]

	JNC 8	2017 ACC/AHA
BP Classification	Not addressed	Normal: < 120/80 mmHg Elevated: 120-129/<80 mmHg Stage 1 HTN: 130-139/80-89 Stage II HTN: ≥140/90 mmHg
Threshold for Initiating Drug Therapy (mmHg)	Age < 60 years: 140/90 Age ≥ 60 years: 150/90 Adults with CKD: 140/90 Adults with DM: 140/90	Adults with clinical CVD or 10-year ASCVD risk ≥ 10%: 130/80 Adults with no CVD and 10-year ASCVD risk < 10%: 140/90
Goal BP (mmHg)	Age < 60 years: < 140/90 Age ≥ 60 years: <150/90 Adults with CKD: <140/90 Adults with DM: < 140/90	Age <65 years: <130/80 Age ≥ 65 years: SBP<130
First Line Therapy (General)	One of the following: thiazide, CCB, ACE-I, or ARB	One of the following: thiazide, CCB, ACE-I, or ARB; start 2 agents from different classes for stage II HTN
Preferred Agents in Special Populations	Black race: Thiazide or CCB CKD: ACE-I or ARB	Compelling indications recommended to guide prescribing (e.g., BB in HFrEF; ACE-I in albuminuria, CKD, or DM)

Key: ACC=American College of Cardiology, ACE-I=angiotensin-converting enzyme inhibitor, AHA=American Heart Association, ARB=angiotensin receptor blocker, ASCVD = atherosclerotic cardiovascular disease, BB=beta blocker, BP=blood pressure, CCB=calcium channel blocker, CKD= chronic kidney disease, CVD=cardiovascular disease, DM = diabetes mellitus, HTN=hypertension, HFrEF= heart failure with reduced ejection fraction, JNC=Joint National Committee, SBP=systolic blood pressure

Initiation of Drug Therapy

According to the 2017 ACC/AHA guidelines, the decision to initiate antihypertensive therapy should be based on patients' 10-year atherosclerotic cardiovascular disease (ASCVD) risk, as well as BP readings, rather than BP alone.[1] This approach is practical given the association between uncontrolled hypertension and ASCVD, but it is the first time cardiovascular (CV) risk influences the treatment algorithm for hypertension. Patients with a history of clinical cardiovascular disease (CVD) or a calculated 10-year ASCVD risk of at least 10% should start an antihypertensive drug once their BP is greater than or equal to 130/80 mmHg. For convenience, one may assume patients with diabetes mellitus (DM) or chronic kidney disease fall into this high-risk category. Patients with lower CV risk are granted more leeway; drug therapy is not indicated until their BP reaches 140/90 mmHg or above.

Literature Supporting New BP Targets

Another major change proposed by the new guidelines is the shift toward stricter BP control. Whereas JNC 8 promoted more lenient BP goals than previous iterations, especially among the elderly, the 2017 ACC/AHA guidelines recommend a target BP less than 130/80 for all patients regardless of age and comorbidities.[1,3] Table 2 summarizes the four major trials influencing this recommendation.

The most robust evidence comes from the Systolic Blood Pressure Intervention Trial (SPRINT), a large randomized controlled trial that demonstrated a decreased incidence of adverse CV outcomes with a target SBP less than 120 mmHg compared to a target SBP less than 140 mmHg.[5] SPRINT excluded patients with DM, limiting the generalizability of the results. To determine whether intense BP control confers CV benefit in patients with DM, Buckley and colleagues performed a subgroup analysis of patients from the ACCORD-BP trial who otherwise would have been eligible for SPRINT apart from their history of type 2 DM and found similar results.[6] Further, no differences in outcomes were observed when patients from this post hoc analysis were pooled with those from SPRINT, suggesting the CV benefits of intensive BP control are independent of patients' diabetes status. Of note, the American Diabetes Association still recommends a target BP less than 140/90 mmHg for most patients with diabetes, although they note lower targets (i.e., <130/80 mmHg) may be considered for patients with high ASCVD risk if tolerated.[7]

The 2017 ACC/AHA guidelines recommend a higher goal SBP than what was studied in SPRINT (<130 mmHg vs. <120 mmHg) to account for the decreased accuracy of real-word BP readings outside of controlled trials.[1] This goal is also supported by the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, a randomized open-label study designed to evaluate different SBP targets in adults who had a symptomatic, MRI-confirmed lacunar stroke within the previous 180 days.[8] A stricter SBP target (<130 mmHg vs. 130-149 mmHg) did not confer a difference in the incidence of recurrent stroke; however, it was associated with a significantly lower incidence of intracranial hemorrhage. The Heart Outcomes Prevention Evaluation (HOPE)-3 trial did not evaluate a particular BP goal, but it is cited by the new guidelines since the subgroup with the highest baseline SBP (>143.5 mmHg) demonstrated improved CV outcomes.[9] HOPE-3 assessed the impact of a fixed dose of candesartan and hydrochlorothiazide compared to placebo in men at least 55 years old and women at least 60 years old with intermediate CV risk. A recent meta-analysis of 42 trials and 144,220 patients further supports the recommendation of more intensive BP control.[10] Bundy and colleagues found a direct relationship between mean SBP and CVD, as well as all-cause mortality. Average achieved SBP of 120-124 mmHg was associated with the lowest risk, supporting the 2017 ACC/AHA BP target.

Pharmacotherapy

First line antihypertensive therapy should be selected from one of four medication classes: thiazide diuretics, angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers, or dihydropyridine calcium channel blockers, as these medication classes have demonstrated improved CV outcomes in clinical trials.[1] These medication class recommendations are similar to the 2014 guidelines.[3] For patients with stage II hypertension, initiation of two medications from two different classes is recommended as initial therapy.[1] Specific medication considerations new to the 2017 guidelines include recommending chlorthalidone as the preferred thiazide-type diuretic, due to proven CV risk reduction.[11] Compelling indications for antihypertensive initiation are similar to the recommendations in JNC 7, including use of beta blockers in heart failure with reduced ejection fraction or previous myocardial infarction and use of ACE-I in patients with chronic kidney disease or DM with albuminuria.[1]

Resistant hypertension management includes maximization of thiazide diuretics (chlorthalidone or indapamide preferred) or addition of spironolactone.[1] Initiation of spironolactone in patients with resistant hypertension has demonstrated superior improvements in BP compared to doxazosin or bisoprolol.[12]

Application of the 2017 guideline recommendations on inpatient care is not extensively described.[1] It may be reasonable to apply the recommended BP treatment goals to hospitalized patients after consideration of patient specific factors, such as comorbid conditions and tolerance of the treatment goals. Recommendations are provided on inpatient management of hypertension, specifically hypertensive crises, defined as a SBP greater than 180 mmHg or DBP greater than 120 mmHg. Similar to previous guidance documents, reinitiation of oral agents in the absence of end organ damage is recommended.[1,13] Patients with evidence of end organ damage are defined as hypertensive emergencies and pharmacotherapy should include a titratable continuous infusion.[1]

Conclusions

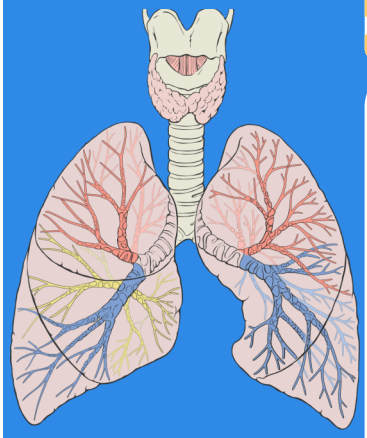
The 2017 ACC/AHA hypertension guidelines represent a shift to stricter hypertension definitions and goals. Recent studies, especially SPRINT, have led to these changes. The impact on management of hypertension is projected to be significant with the potential for improved patient outcomes.

Table 2. Primary Literature Supporting BP Targets[5,6,8,9]

Study	Intervention	Outcomes
SPS3 (2013)	Target SBP <130 mmHg vs. target SBP 130-149 mmHg At 1 year, lower-target group achieved mean SBP of 127 mmHg with average of 2.4 antihypertensive agents; higher-target group achieved mean SBP of 138 mmHg with average of 1.8 antihypertensives	N = 3,020 Primary: No significant difference in the incidence of stroke Secondary: Increased incidence of intracerebral hemorrhage in higher-target group (HR, 0.37; 95% CI, 0.15-0.95; P=0.03; NNH=142) No significant difference in the incidence of MI, major vascular events, or death
SPRINT (2015)	Target SBP < 120 mmHg (intensive group) vs. target SBP < 140 mmHg (standard group) Intensive group achieved mean SBP of 121.5 mmHg with average of 2.8 antihypertensives; standard group achieved mean SBP of 134.6 mmHg with average of 1.8 antihypertensive agents	N= 9,361 Primary: 25% RRR in composite endpoint (MI, ACS, stroke, acute decompensated HF, or death from CV causes) in intensive group vs. standard group (HR, 0.75; 95% CI, 0.64 to 0.89; P<0.001; NNT = 61) Secondary: 43% RRR in death from CV cause in intensive group (HR, 0.57; 95% CI, 0.38 to 0.85; P=0.005; NNT = 172) 27% RRR in death from any cause in intensive group (HR, 0.73; 95% CI, 0.6 to 0.9; P=0.003; NNT = 90) Significantly greater incidence of hypotension, syncope, electrolyte abnormalities, and AKI in the intensive group
HOPE-3 (2016)	Candesartan 16 mg + hydrochlorothiazide 12.5 mg vs. placebo Mean difference in BP: -6/3 mmHg (baseline 138.1/81.9 mmHg)	N=12,705 Primary: No differences between groups in either co-primary composite endpoints (death from CV cause/nonfatal MI/nonfatal stroke +/- cardiac arrest/heart failure/revascularization) 24-27% RRR in both composite outcomes in subgroup with highest baseline SBP (>143.5 mmHg); NNT = 58 and 57 for the first and second composite outcomes, respectively Secondary: No differences in components of composite endpoints, total mortality, or total CV events (post hoc outcome) Significantly more patients in treatment group withdrew from study due to hypotension/dizziness/lightheadedness(NNH = 71)
ACCORD-BP Subgroup Analysis (2017)	Target SBP < 120 mmHg (intensive group) vs. target SBP < 140 mmHg (standard group) Intensive group achieved mean SBP of 120.1 mmHg; the standard group achieved a mean SBP of 133.5 mmHg	N=1,284 Primary: 21% RRR in composite endpoint (MI, revascularization, stroke, HF, or death from CV causes) in intensive group vs. standard group (HR, 0.79; 95% CI, 0.65 to 0.96; P=0.02; NNT=15) Secondary: No differences in components of composite endpoints or death from any cause Greater incidence of treatment-related serious adverse events in the intensive group (4.1% vs. 2.1%; P=0.003; NNT=50)

Key: 95% CI = 95% confidence interval, ACS = acute coronary syndrome, AKI = acute kidney injury, ASCVD = atherosclerotic cardiovascular disease, BP=blood pressure, CV = cardiovascular, HF = heart failure, HR = hazard ratio, ICH = intracranial hemorrhage, MI = myocardial infarction, NNT = number needed to treat, SBP = systolic blood pressure, RRR = relative risk reduction

Acknowledgements: Article peer-reviewed and edited by Sarah Nisly, PharmD, BCPS



"With an increase in inhaler options and a shift in treatment recommendations, pharmacists are uniquely poised to facilitate optimal inhaler selection while considering patient specific factors such as cost, frequency, and inhaler technique"

A Breath of Fresh Air: Updates in COPD Management

By: Denise Kelley, PharmD, BCPS, AAHIVP and Emmeline Tran, PharmD, BCPS

The update to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines in 2017 presented a few new revisions and recommendations. Specifically, the assignment of "ABCD" categories is based on symptoms and exacerbations, and spirometric grades are no longer included.[1] The refinement of the assessment tool was based on studies finding that the tool did not function any better than spirometric grades in predicting mortality or other significant outcomes in chronic obstructive pulmonary disease (COPD).[1] Additionally, the 2017 guidelines introduced a shift in preferred pharmacological agents and personalization of treatment with escalation and de-escalation strategies (Figure 1).[1] These changes remained consistent in the 2018 update.[2] The evidence, with a focus on primary literature, behind these pharmacological recommendations will be further discussed.

Figure 1. Comparison of pharmacological treatment algorithms[1, 3]

Group	2017	2016	
		First Choice	Alternative Choice
A	Continue, stop, or try alternative ↑ bronchodilator	SAMA prn ***OR*** SABA prn	LAMA ***OR*** LABA ***OR*** SABA + SAMA
B	LAMA + LABA ↑ LAMA OR LABA	LAMA ***OR*** LABA	LAMA + LABA
C	LAMA + LABA LABA + ICS ↖ ↗ LAMA	LABA + ICS ***OR*** LAMA	LAMA + LABA ***OR*** LAMA + PDE-4 ***OR*** LABA + PDE-4
D	roflumilast or macrolide* ↑ LAMA + LABA + ICS ↑↓ ↖ LAMA → LAMA + LABA ← LABA + ICS	LABA + ICS ***AND/OR*** LAMA	LAMA + LABA + ICS ***OR*** LABA + ICS + PDE-4 ***OR*** LAMA + LABA ***OR*** LAMA + PDE-4

preferred treatment

*to be considered depending on clinical situation; roflumilast if FEV_1 < 50% predicted and patient has chronic bronchitis, macrolide in former smokers

FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; PDE-4 = phosphodiesterase-4 inhibitor; SABA = short-acting beta agonist; SAMA = short-acting muscarinic antagonist

Evidence

Long-Acting Bronchodilators

COPD drug therapy management centers on bronchodilation with inhaled beta$_2$ agonists and/or inhaled muscarinic antagonists and inflammation reduction with inhaled corticosteroids (ICS). While all modalities may be necessary in reducing COPD exacerbations for some patients, identifying an evidence-based, step-wise approach has been lacking until recent years. The GOLD guidelines previously recommended initiating a long-acting beta$_2$ agonist (LABA) or long-acting muscarinic antagonist (LAMA) with little guidance on preference.[3] Several studies now support using a LAMA as the preferred therapy over using a LABA.[4, 5] In the POET-COPD study, tiotropium 18 mcg once daily increased the time to first exacerbation compared with salmeterol 50 mcg twice daily (187 days vs. 145 days, $p < 0.001$) in patients with moderate to severe COPD.[4] Similar results were found in the INVIGORATE analysis, which was designed as a non-inferiority study of indacaterol 150 mcg once daily versus tiotropium 18 mcg once daily.[5] Although indacaterol proved non-inferior to tiotropium in the primary outcome of trough forced expiratory volume in 1 second (FEV_1) at week 12, tiotropium showed superiority in annual rate of exacerbations (0.73 vs. 0.90, $p < 0.0001$) and longer time to first moderate to severe exacerbation ($p = 0.0012$). The absolute rates of exacerbations in this study were small raising the question of clinical relevance. However, given the results of both studies, initiating a LAMA is now the recommended, first-line approach for patients with COPD classified as group C.[1]

In light of the evidence supporting LAMA therapy, updates to combination therapy have also been investigated. Use of a LABA-ICS was previously suggested as a dual-therapy approach.[3] However, recent studies have examined the utility of a LAMA-LABA combination. The FLAME study assessed a head-to-head comparison of LAMA-LABA dual therapy versus LABA-ICS dual therapy.[6] Patients with moderate to severe COPD were randomized to receive indacaterol-glycopyrronium 110-50 mcg once daily versus salmeterol-fluticasone 50-500 mcg twice daily with a primary outcome of annual rate of all COPD exacerbations. The LAMA-LABA combination showed both non-inferiority and superiority in reducing the annual COPD exacerbation rate (3.59 vs. 4.03, $p = 0.003$). Time to first exacerbation rate was also longer in the indacaterol-glycopyrronium group compared with the salmeterol-fluticasone group (71 days vs. 51 days with a hazard ratio of 0.84; $p < 0.001$). The promising results of using a LAMA-LABA combination over LAMA monotherapy and LABA-ICS dual therapy led to the shift in COPD treatment, making a LAMA-LABA combination the now preferred treatment for group D patients.

Despite the positive clinical outcomes with LAMA-LABA combination therapy, one concerning adverse event noted is potential associations with cardiovascular (CV) events. In a nested case-control study from the Taiwan National Health Insurance Research Database from 2007-2011, an approximate 1.5 fold increase in CV risk was associated with the new initiation of LABA or LAMA inhalers, regardless of baseline CV risk status.[7] Additional analyses of this correlation in the United States are necessary to help further guide preferential treatment options in patients with COPD.

Inhaled Corticosteroids

The clinical utility of ICS for the treatment of COPD is not clearly defined. The TORCH study established a LABA-ICS combination as a fundamental therapy choice in patients with moderate to severe COPD.[8] This study found that salmeterol-fluticasone 50-500 mcg twice daily was associated with a statistically significant decrease in the annual rate of moderate or severe exacerbations compared with placebo, salmeterol 50 mcg twice daily monotherapy, and fluticasone 500 mcg twice daily monotherapy (0.85 vs. 1.13, 0.97, and 0.93 respectively; $p < 0.02$). However, this was at the expense of an increased rate of pneumonia compared with placebo and salmeterol (19.6% vs. 12.3% and 13.3% respectively; $p < 0.001$).

An increased rate of pneumonia in patients receiving LABA-ICS combination therapy was also observed in the INSPIRE and FLAME studies.[6, 9] The INSPIRE study examined patients with severe COPD receiving either salmeterol-fluticasone 50-500 mcg twice daily or tiotropium 18 mcg once daily. No difference was found in the annual rate of exacerbations between patients receiving salmeterol-fluticasone and tiotropium (1.28 vs. 1.32; $p = 0.656$). However, in the salmeterol-fluticasone group, a statistically significant lower rate of mortality (6% vs. 3%; $p = 0.032$) and a statistically significant increase in the rate of pneumonia (8% vs. 4%) was observed, with a hazard ratio for time to reported pneumonia of 1.94 ($p = 0.008$). The FLAME trial further corroborated the increased incidence of pneumonia in patients on ICS therapy (salmeterol-fluticasone group, 4.8% vs. indacaterol-glycopyrronium group, 3.2%; $p = 0.02$).[6] Consequently, due to the increased risk for developing pneumonia with the use of an ICS, the guidelines make a preferential recommendation to escalate with the addition of a second long-acting bronchodilator rather than to a LABA-ICS combination in groups C and D patients with persistent exacerbations.[1]

De-escalation of therapy, specifically withdrawal of ICS, has been investigated with equivocal findings on lung function, frequency of exacerbations, and quality of life.[10] Data supporting the potential to withdraw ICS come from the WISDOM trial. Patients were randomized to triple therapy of tiotropium 18 mcg once daily, salmeterol 50 mcg twice daily, and fluticasone 500 mcg twice daily versus triple therapy with a stepwise reduction in fluticasone dose every 6 weeks. The withdrawal group was deemed noninferior to the continuation group since the upper limit of the confidence interval was below the prespecified noninferiority margin of 1.20. However, there was a statistically significant greater reduction in FEV_1 in the withdrawal group at 52 weeks (-43 mL; $p = 0.001$). The minimal clinically important difference in FEV_1 is considered to be 100 mL improvement.[11] Therefore, it is unknown what this magnitude of reduction may mean clinically long-term. Furthermore, no guidance has been provided on the optimal process to withdrawing ICS. The recommendations by the guidelines directing withdrawal of ICS is derived mainly from concerns of adverse effects, lack of efficacy, and, although the data is limited, no significant harm found from withdrawal.[1]

Blood eosinophil counts may be considered as a parameter to support the use of ICS in patients with COPD. Specifically, studies have found that patients with blood eosinophil counts greater than or equal to 2% may benefit from ICS therapy.[12] Furthermore, blood eosinophil counts may also help guide which patients may not tolerate ICS withdrawal. A post-hoc analysis of the WISDOM trial observed that patients with blood eosinophil counts of greater than or equal to 4% experienced an increased rate of exacerbations.[13] Conversely, the FLAME trial found that regardless of blood eosinophil count, the rates of moderate or severe exacerbations and all exacerbations were significantly lower in the indacaterol-glycopyrronium group than in the salmeterol-fluticasone group.[6, 14] More data is needed to help guide the clinical utility of blood eosinophil counts in determining ICS benefit in patients with COPD.

Practice Considerations

An influx in inhaled LAMA, LABA, and LAMA-LABA combination therapy options achieved FDA approval in the last several years, including the first nebulized LAMA approved in late 2017 (Table 1). With an increase in inhaler options and a shift in treatment recommendations, pharmacists are uniquely poised to facilitate optimal inhaler selection while considering patient specific factors such as cost, frequency, and inhaler technique. Following the success of indacaterol-glycopyrronium in the FLAME trial, physicians may opt for this inhaler combination.[6] However, the approved United States product contains 27.5-15.6 mcg for twice daily administration which is lower than the 110-50 mcg once daily strategy used in the study. Cost is a significant barrier to these inhaler therapies, where careful consideration and coordination with respective insurance plans are necessary.

In patients who require more than one type of inhaled medication class, switching from individual inhalers to combination inhalers may be cost effective. In September 2017, the FDA approved the first triple therapy inhaler containing a LAMA, LABA, and ICS that may prove cost effective for select patients and improve patient compliance. While potential adverse effects associated with various inhaler types continue to be elucidated, pharmacists should be mindful of the cardiovascular concerns of LAMA-LABA combinations as well as the pneumonia risk associated with ICS.

In summary,

- All patients with COPD should receive a short acting bronchodilator to be used as needed.
- For moderate COPD, an inhaled LAMA is the preferred initial treatment. If additional therapy is needed, a LAMA-LABA combination is preferred.
- The addition of an ICS may be considered in severe disease not controlled by LAMA-LABA dual therapy, or in patients with overlapping asthma symptoms.

Table 1. Comparison of FDA-approved COPD inhalers[15]

Medication	Brand(s)	Dosing Frequency	Cost*
Monotherapy: LABA			
Indacaterol	Arcapta® Neohaler®	Once daily	$243.60
Olodaterol	Striverdi® Respimat®	Once daily	$181.61
Salmeterol	Serevent® Diskus®	Twice daily	$351.63
Monotherapy: LAMA			
Aclidinium	Tudorza® Pressair®	Twice daily	$322.17
Glycopyrrolate	Seebri™ Neohaler® Lonhala™ Magnair™	Twice daily	$394.20 not available
Tiotropium	Spiriva® Handihaler® Spiriva® Respimat®	Once daily	$368.20 $368.20
Umeclidinium	Incruse® Ellipta®	Once daily	$324.06
Combination: LABA-LAMA			
Formoterol/Glycopyrrolate	Bevespi® Aerosphere®	Twice daily	$334.62
Indacaterol/Glycopyrrolate	Utibron™ Neohaler®	Twice daily	$340.20
Olodaterol/Tiotropium	Stiolto® Respimat®	Once daily	$340.93
Vilanterol/Umeclidinium	Anoro® Ellipta®	Once daily	$368.20
Combination: LABA-ICS			
Formoterol/Budesonide	Symbicort®	Twice daily	$308.68
Salmeterol/Fluticasone	Advair® Diskus® Advair® HFA	Twice daily	$475.32 $475.32
Vilanterol/Fluticasone	Breo Ellipta®	Once daily	$321.74
Combination: ICS-LAMA-LABA			
Fluticasone furoate/ Umeclidinium/Vilanterol	Trelegy Ellipta®	Once daily	$530.00

*U.S. medication pricing by Elsevier, accessed November 2017. Wholesale cost for 30-day supply of highest strength, of generic if available.
ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist

Acknowledgements: Article peer-reviewed and edited by Heather Kehr, PharmD, BCPS and Lauren McCluggage, PharmD, BCPS

PRN Member Accomplishments

Publications:

Paul M. Boylan:

Boylan PM, Joseph T, Hale GM, Moreau C, Seamon M, Jones R. Development of chronic obstructive pulmonary disease and heart failure self-management kits for outpatient transitions of care. Consult Pharm. 2018;33(3):145-151.

Boylan P, Trinh K, Helms J, Ghoubrial-Waibel R, Mege J. Integration of transitions of care pharmacist services within an accredited pulmonary rehabilitation clinic. Pharmacotherapy. 2017;37(12):e214.

Luder H, Zavadsky A, Bukowitz A, Baumann A, **Boylan PM**, Croley KS, Fu D, Kelling SE, Winder M, Register D. Transitions of care case examples resource. American Pharmacists Association: Washington, DC. Pub June 2017. Available from: www.pharmacist.com/transitions-care

Vi Gilmore:

Sowell AJ, Pherson EC, Almuete VI, Gillespie JV, **Gilmore V**, Jensen M, Nehra R, Durand KM, Nesbit TW, Swarthout MD. Expansion of inpatient clinical pharmacy services through reallocation of pharmacists. Am J Health-Syst Pharm 2017;74:1806-13.

Sarah L. Anderson:

Anderson SL, Marrs JC. The Role of the Pharmacist in Heart Failure Transition of Care. Adv Ther 2018 [Epub ahead of print: https://doi.org/10.1007/s12325-018-0671-7].

Anderson SL, Marrs JC. Direct oral anticoagulant (DOAC) use in valvular heart disease. Clinical Medicine Insights: Therapeutics 2018;10:1-6.

Anderson SL, Trujillo JM, Anderson JE, Tanenberg R. Switching basal insulins – practical recommendations for health care providers. Postgrad Med 2017;1-10. doi: 10.1080/00325481.2018.1419048. [Epub ahead of print]

Jon P. Wietholter:

Wietholter JP, Grey C, Howard C, Johnson BN, Sween R, Rowlands AE. Interprofessional collaborative practice through an adult medicine based simulation. J Interprof Educ Pract. 2017;9:21-26.

Jennifer Twilla:

Cutshall BT, **Twilla JD**, Olinger AS, Oliphant CS. A review on cardiovascular effects of newer hypoglycaemic medications. Ann Med. 2017 Nov;49(7):603-612.

Owens RE, **Twilla JD**, Self TH, Alshaya AI, Metra CJ, Cummings C, Oliphant CS. β-Blockade in Heart Failure With Reduced Ejection Fraction: Does Heart Rate Control Influence Readmissions? J Pharm Pract. 2018 Feb;31(1):40-45.

Nicole J. Asal:

Asal NJ, Poyant J. Role and impact of student pharmacists and a pharmacist on an international interprofessional medical brigade. Currents in Pharmacy Teaching and Learning. February 2018. (In Press).

Julie A. Murphy:

Murphy JA, Schroeder MN, Rarus RE, Yakubu I, McKee SOP, Martin SJ. Implementation of a cardiac transitions of care pilot program: a prospective study of inpatient and outpatient clinical pharmacy services for patients with heart failure exacerbation or acute myocardial infarction. J Pharm Pract 2018 Jan 1:897190017743129. doi: 10.1177/0897190017743129. [Epub ahead of print].

Murphy JA, Sheridan EA. Evidence Based Review of Pharmacotherapy for Opioid-Induced Constipation in Noncancer Pain. Ann Pharmacother 2017 (Oct 1); doi: 10.1177/1060028017739637. [Epub ahead of print]

PRN Member Accomplishments

Publications:

Mary Elizabeth Briand:

Clark KE, **Briand ME**, Kapoor O, Pirasteh A. Impact of a standardized beta-lactam allergy questionnaire on aztreonam use. J Pharm Pract. 2018 Jan 1: 897190018758557. doi: 10.1177/0897190018758557. [Epub ahead of print]

Ryan E. Owens:

Roberts MZ, Farley TM, **Owens RE**. Comparison of the safety and effectiveness of apixaban versus warfarin in patients with severe renal impairment: An alternative viewpoint. Pharmacotherapy. 2017 Oct;37(10):e107-108.

Owens RE, Twilla JD, Self TH, Alshaya AI, Metra CJ, Cummings C, Oliphant CS. β-Blockade in Heart Failure With Reduced Ejection Fraction: Does Heart Rate Control Influence Readmissions? J Pharm Pract. 2018 Feb;31(1):40-45.

Shah SP, Self TH, Bradsher RW 3rd, **Owens RE**. Clarithromycin-nifedipine-induced acute kidney injury. Nurse Pract. 2017 Sep;42(9):49-51.

Rachel Flurie:

Gravatt LAH, **Flurie RW**, Lajthia E, Dixon DL. Clinical guidance for managing statin and antimicrobial drug-drug interactions. Curr Atheroscler Rep. 2017;19(46). DOI: 10.1007/s11883-017-0682-x

Flurie RW and Brophy DF. Chronic hyperkalemia: evolving options for a common problem. Powerpak.com. https://www.powerpak.com/course/preamble/115972. Published December 29, 2017. Accessed February 5, 2018.

Promotions:

Angela Miller: Adjunct Assistant Clinical Professor- University of Kansas: Department of Pharmacy Practice

Awards:

Erin McCreary: 2017 ACCP Adult Medicine PRN Best Poster Award

Diana Sobieraj: 2017 ACCP New Investigator Award

Jennifer Twilla: 2017 ACCP Adult Medicine PRN Clinical Practice Award

Julie A. Murphy: 2017 ACCP Education and Training PRN Best Poster Award

Nicole J. Asal: 2017 Rhode Island Pharmacists Association Distinguished Young Pharmacist Award

Beth H. Resman-Targoff: 2018 National Rho Chi Honor Society Faculty Advisor Award

Rachel Flurie: 2017 Virginia Health-System Pharmacists New Practitioner Award

Grants:

Diana Sobieraj: Treatment of Depression in Older Adults. Co-Principal Investigator. Funding Agency: AHRQ, $380,000

Other Notable Achievements:

Beth H. Resman-Targoff: Elected to serve on the Association of Rheumatology Health Professionals Membership and Nominations Committee

Andrew Miesner: Completed the SIDP Antimicrobial Stewardship Certificate Program

References:

DM

1. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes. Diabetes Care. 2018; 41(S1):S73-S85.
2. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes. Diabetes Care. 2018; 41(S1):S86-S104.
3. Guidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. U.S. Food and Drug Administration. December 2008.
4. Marx N, McGuire DK, Perkovic V, et al. Composite Primary End Points in Cardiovascular Outcomes Trials Involving Type 2 Diabetes Patients: Should Unstable Angina Be Included in the Primary End Point? *Diabetes Care*. 2017;40(9):1144-1151.
5. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317-1326.
6. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369 (14):1327-1335.
7. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2015;373 (3):232-242.
8. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 2015;373 (23):2247-2257..
9. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):311-322..
10. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375 (19):1834-1844..
11. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2017;377(13):1228-1239..
12. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373 (22):2117-2128.
13. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644 -657.
14. Jardiance® [package insert]. Ridgefield, CT: Boeringer Ingelheim Pharmaceuticals Inc, 2017.
15. Victoza® [package insert]. Painsboro, NJ: Novo Nordisk Inc, 2017.
16. Cefalu WT, Kaul S, Gerstein HC, et al. Diabetes Care. 2018; 41:14-21.

HTN

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017.
2. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42(6):1206-52.
3. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311(5):507-20.
4. Muntner P, Carey RM, Gidding S, et al. Potential US Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. *Circulation* 2018;137(2):109-18.
5. Group SR, Wright JT, Jr., Williamson JD, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2015;373(22):2103-16.
6. Buckley LF, Dixon DL, Wohlford GFt, et al. Intensive Versus Standard Blood Pressure Control in SPRINT-Eligible Participants of ACCORD-BP. *Diabetes Care* 2017;40(12):1733-8.
7. American Diabetes A. 9. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018;41 (Suppl 1):S86-S104.
8. Group SPSS, Benavente OR, Coffey CS, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013;382(9891):507-15.

9. Lonn EM, Bosch J, Lopez-Jaramillo P, et al. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *N Engl J Med* 2016;374(21):2009-20.
10. Bundy JD, Li C, Stuchlik P, et al. Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-analysis. *JAMA Cardiol* 2017;2(7):775-81.
11. Officers A, Coordinators for the ACRGTA, Lipid-Lowering Treatment to Prevent Heart Attack T. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288(23):2981-97.
12. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015;386(10008):2059-68.
13. Marik PE, Varon J. Hypertensive crises: challenges and management. *Chest* 2007;131(6):1949-62.

COPD

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org. Accessed March 5, 2018.
2. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. Available from: http://goldcopd.org. Accessed March 30, 2018.
3. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. Available from: http://goldcopd.org. Accessed March 30, 2018.
4. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med.* Mar 24 2011;364(12):1093-1103.
5. Decramer ML, Chapman KR, Dahl R, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. *Lancet Respir Med.* Sep 2013;1(7):524-533.
6. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. *N Engl J Med.* Jun 9 2016;374(23):2222-2234.
7. Wang MT, Liou JT, Lin CW, et al. Association of Cardiovascular Risk With Inhaled Long-Acting Bronchodilators in Patients With Chronic Obstructive Pulmonary Disease: A Nested Case-Control Study. *JAMA Intern Med.* Feb 1 2018;178(2):229-238.
8. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med.* Feb 22 2007;356(8):775-789.
9. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med.* Jan 1 2008;177(1):19-26.
10. Yawn BP, Suissa S, Rossi A. Appropriate use of inhaled corticosteroids in COPD: the candidates for safe withdrawal. *NPJ Prim Care Respir Med.* Sep 29 2016;26:16068.
11. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. *Am J Respir Crit Care Med.* Feb 1 2014;189(3):250-255.
12. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med.* Jun 2015;3(6):435-442.
13. Watz H, Tetzlaff K, Wouters EF, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med.* May 2016;4(5):390-398.
14. Roche N, Chapman KR, Vogelmeier CF, et al. Blood Eosinophils and Response to Maintenance Chronic Obstructive Pulmonary Disease Treatment. Data from the FLAME Trial. *Am J Respir Crit Care Med.* May 1 2017;195(9):1189-1197.
15. Clinical Resource, Inhalers for COPD. *Pharmacist's Letter/Prescriber's Letter.* January 2018. Accessed: March 5, 2018.