Hyperlipidemia and COPD: 2 Old Problems with New Therapies and Goals

Activity Number: 0217-0000-16-116-L01-P 1.50 hours of CPE credit; Activity Type: An Application-Based Activity

Monday, October 24, 2016

9:15 a.m. to 10:45 a.m.

Great Hall 3

Moderator: E. Kelly Hester, Pharm. D., FCCP, BCPS

Associate Clinical Professor, Department of Pharmacy Practice, Auburn University Harrison School of Pharmacy, Auburn, Alabama

Agenda

9:15 a.m.	Is 50 the New 70? Exploring the Value of Intensified LDL reduction with PCSK-9 Inhibitors and Ezetimibe *Tran H. Tran, Pharm. D., BCPS* Associate Professor, Midwestern University, Chicago College of Pharmacy, Downers Grove, Illinois
10:00 a.m.	Update in COPD Pharmacotherapy: Is New Better? *Christopher K. Finch, Pharm. D., BCPS* Director of Pharmacy, Methodist University Hospital; Associate Professor, University of Tennessee College of Pharmacy, Memphis, Tennessee

Conflict of Interest Disclosures

Christopher K. Finch: no conflicts to disclose
E. Kelly Hester: no conflicts to disclose
Tran H. Tran: no conflicts to disclose

Learning Objectives

1. Explain the relationship between serum LDL level and residual cardiovascular diseases.
2. Evaluate the literature describing the use of the PSCK-9 inhibitors for reducing cardiovascular disease.
3. Interpret the literature pertaining the use of ezetimibe for reducing cardiovascular disease.
4. Construct an evidence-based pharmacotherapy regimen for reducing residual cardiovascular disease in at risk patients.
5. Compare and contrast the pharmacological and cost differences with new therapy options for COPD compared to older medications.
6. Discuss the evidence-based outcomes of newer pharmacologic options based on clinical trials compared to older medications.
7. Explain the role of new agents in the medical management of COPD.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am

Is 50 the new 70? Exploring the value of intensified LDL reduction with PCSK-9 inhibitors and ezetimibe

Tran H. Tran, Pharm. D., BCPS
Associate Professor
Midwestern University
Chicago College of Pharmacy
Downer's Grove, IL
October 24, 2016

Conflict of Interest

- None to disclose

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CVD Remains an Area of High Unmet Need

High Morbidity, Mortality, and Cost	• CVD remains the leading cause of death in the US accounting for 1 out of every 7 deaths • Costs > $320 billion each year
Suboptimal LDL Management	• Despite effective treatments like statins, many patients are not achieving optimal LDL-C levels
Statin Intolerance	• Statin intolerance occurs in ~ 10–20% of patients and commonly results in treatment discontinuation
Limited Treatment Options	• Beyond statins, existing nonstatin agents provide only modest LDL-C reduction

CVD = cardiovascular disease; LDL = low-density lipoprotein; LDL-C = LDL-cholesterol.
Mozaffarian D, et al. *Circulation*. 2015; 131(4):e29-322; CDC. Heart Disease Facts. www.cdc.gov/heartdisease/facts.htm. Accessed 3/24/15; Go AS, et al. *Circulation*. 2014;129(3):E28-E292; Rosenson RS, et al. *J Clin Lipidol*. 2014;8(3 Suppl):S58-S71. PRIME[e].

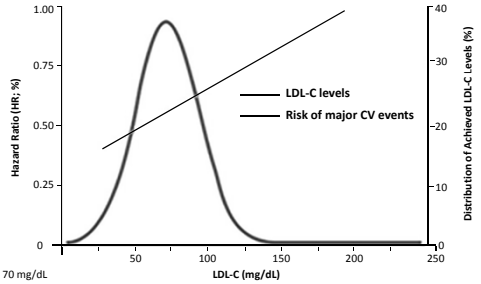
ACC/AHA 2013 Guidelines: 4 Statin Benefit Groups and Intensity of Statin Therapy

Secondary Prevention Clinical ASCVD	• Age ≤ 75: High-intensity statin • Age > 75: Moderate-intensity statin
Primary Prevention LDL-C ≥ 190 mg/dL	• High-intensity statin
Primary Prevention Age 40–75 with diabetes and LDL 70–189 mg/dL, no clinical ASCVD	• Low risk (10-year risk < 7.5%): Moderate-intensity statin • High risk (10-year risk ≥ 7.5%): High-intensity statin
Primary Prevention Age 40–75 with no diabetes or clinical ASCVD, LDL 70–189 mg/dL, estimated 10-year ASCVD ≥ 7.5%	• Consider moderate- or high-intensity statin

Stone NJ, et al. *Circulation*. 2013;129(25 Suppl 2):S1-S45.

Despite Treatment with High-Dose Statins, Many Patients Do Not Achieve Goal*

On-Statin LDL-C Levels and Risk of Major Cardiovascular Events



*< 70 mg/dL
Adapted from: Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485-494. PRIME[e].

PCSK9 inhibitors

Heterozygous FH

- Characterized by high LDLC levels (≥ 190 mg/dL)
- Primarily caused by mutations in LDL-R gene, as well as in APOB or PCSK9 genes
- Believed to occur in one in every 200 individuals
- Leads to 10- to 20-fold lifetime increased risk of heart attack
  - Men with HeFH have a 50% chance of a heart attack by age 50 without treatment and in women there's a 30% chance by age 60

HeFH = heterozygous familial hypercholesterolemia, LDLC = LDL cholesterol, LDL-R = LDL-receptor.

PCSK9: A Compelling New Hypercholesterolemia Target

- The key role of PCSK9 in LDL-C metabolism:
  - Promotes intracellular degradation of hepatic LDL-R
  - Prevents LDL-R recycling to cell surface
  - Reduces LDL-R population on cell surface
  - Reduces LDL clearance from circulation

LDL-R = LDL-receptor.
Lambert G, et al. *J Lipid Res*. 2012;53(12):2515-2524.

Role of PCSK9 in Regulation of LDL-R Expression

FDA Approved PCSK9 Inhibitors:

	Alirocumab	Evolocumab
Indication	Patients with HeFH or clinical atherosclerotic CVD In addition to diet and maximally tolerated statin therapy	
Dosage and administration	• Two different doses: 75 mg or 150 mg dose every 2 weeks • Available in a single 1 mL SQ injection delivered in a single-dose prefilled pen or syringe that patients self-administer	• Two different doses: 140 mg dose every 2 weeks or 420 mg dose every month • Available in a single prefilled SQ autoinjector or on-body infusor with prefilled cartridge

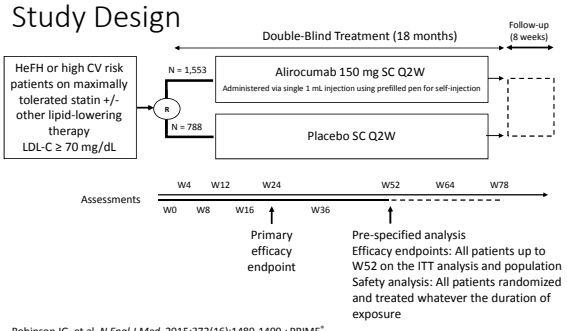
HeFH = heterozygous familial hypercholesterolemia, CVD = cardiovascular disease
FDA News Release. FDA approves Praluent to treat certain patients with high cholesterol. Released July 24, 2015. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455883.htm

Alirocumab: ODYSSEY Trial Program

Type of Study	Trial Name	N	Duration (weeks)		
Moderate CV Risk	MONO	103	24		Not receiving statins
Statin Intolerant	ALTERNATIVE	314	24		
	CHOICE II*	803	24		Moderate statin dose
	CHOICE I*	233	24		
	OPTIONS I	355	52		
High LDL-C	OPTIONS II	305	104		
High CV Risk	COMBO I	316	52		Plus max statin dose
	COMBO II	720	24		
	LONGTERM	2,341	78		
	FH I	471	78		
HeFH	FH II	250	78		
	High FH	105	78		
High CV Risk Recent CV Event	OUTCOMES	18,000	5–6 years	Ongoing	

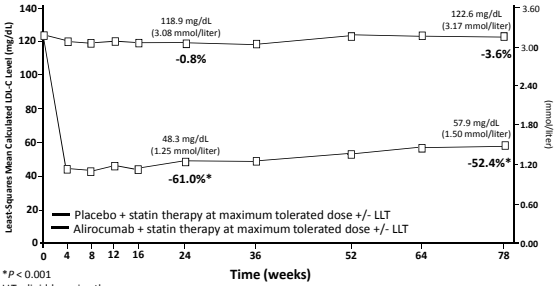
*CHOICE I & II evaluated alirocumab every 2 weeks and monthly.; PRIME®.

Alirocumab: ODYSSEY LONGTERM Study Design



Robinson JG, et al. *N Engl J Med*. 2015;372(16):1489-1499.; PRIME[+].

Alirocumab (ODYSSEY LONGTERM) Calculated LDL-C Levels Over Time (ITT)



*$P < 0.001$
LLT = lipid-lowering therapy.
Robinson JG, et al. *N Engl J Med*. 2015;372(16):1489-1499; PRIME[+].

Alirocumab (ODYSSEY LONGTERM) Safety Analysis

Summary of AEs	Alirocumab (n = 1,550)	Placebo (n = 788)	*P* Value
SAEs	290 (18.7%)	154 (19.5%)	0.66
AE leading to discontinuation	111 (7.2%)	46 (5.8%)	0.26
AE leading to death	8 (0.5%)	10 (1.3%)	0.08
General allergic reaction events	156 (0.1%)	75 (9.5%)	0.71
Treatment-related injection site reactions	91 (5.9%)	33 (4.2%)	0.10
Neurologic events	65 (4.2%)	35 (4.4%)	0.83
Neurocognitive events	18 (1.2%)	4 (0.5%)	0.17

Among patients who received alirocumab, 575 (37.1%) had a calculated LDL-C level of < 25 mg/dL at 2 consecutive measurements. Rates of AEs were similar to those in the overall alirocumab group.

Robinson JG, et al. *N Engl J Med*. 2015;372(16):1489-1499. PRIME[+].

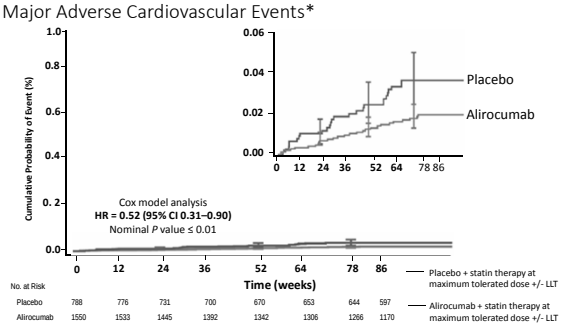
Alirocumab (ODYSSEY LONGTERM) Safety Analysis: Cardiovascular Adverse Events

Cardiovascular AE	Alirocumab (n = 1,550)	Placebo (n = 788)	*P* Value
CHD death	4 (0.3%)	7 (0.9%)	0.26
Non-fatal MI	14 (0.9%)	18 (2.3%)	0.01
Fatal + non-fatal ischemic stroke	9 (0.6%)	2 (0.3%)	0.35
Unstable angina requiring hospitalization	0	1 (0.1%)	0.34
Positively adjudicated CV events, including all those listed above	72 (4.6%)	40 (5.1%)	0.68
Adjudicated major AEs in post-hoc analysis*	27 (1.7%)	26 (3.3%)	0.02

*The post-hoc analysis was not specified in the study protocol. It included the following CV event categories, which also form the endpoint for the ODYSSEY OUTCOMES study: Death from CHD, non-fatal MI, fatal and non-fatal ischemic stroke, and unstable angina requiring hospitalization. "Unstable angina requiring hospitalization" is limited to the unstable angina events with definite evidence of progression of the ischemic condition (strict criteria).

Robinson JG, et al. *N Engl J Med*. 2015;372(16):1489-1499; PRIME[+].

Post-Hoc Analysis of a Subgroup of Adjudicated Major Adverse Cardiovascular Events*



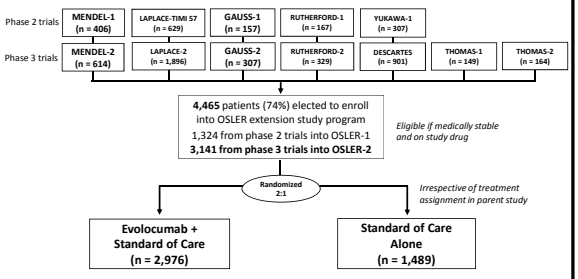
*same primary endpoint as ongoing ODYSSEY OUTCOMES trial.
Robinson JG, et al. *N Engl J Med*. 2015;372(16):1489-1499. PRIME[+].

Evolocumab: Select Trials from the PROFICIO Clinical Trial Program*

Type of Study	Trial Name	N	Duration (weeks)		
Monotherapy	MENDEL-2	614	12		Not Receiving Statins
Statin Intolerant	GAUSS-2	307	12		
	GAUSS-3	500;100	24	Ongoing	
Combination Therapy	LAPLACE-2	1,896	12		Receiving Statin Therapy
High CV Risk	DESCARTES	901	52		
	GLAGOV	950	78	Ongoing	
FH	RUTHERFORD-2 (HeFH)	329	12		
	TESLA (HoFH)	58	12		
	TAUSSIG	250	5 years	Ongoing	
Established CVD	FOURIER	22,500	5 years	Ongoing	

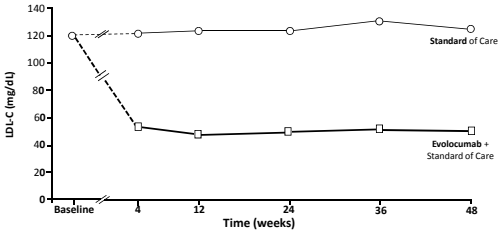
*Evaluated evolocumab every 2 weeks and monthly.
PRIME[+].

Evolocumab: Open-Label Studies of Long-Term Evaluation Against (OSLER-1 and OSLER-2)



Sabatine MS, et al. *N Engl J Med*. 2015;372(16):1500-1509. PRIME[+].

Evolocumab (OSLER-1 and OSLER-2): LDL-C Levels Over Time



No. at Risk						
Standard therapy	1489	394	1388	1376	402	1219
Evolocumab	2976	864	2871	2828	841	2508
Absolute reduction (mg/dL)		60.4	73.4	70.4	72.7	70.5
Percentage reduction		56.3	60.9	58.8	54.0	58.4
P value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Sabatine MS, et al. *N Engl J Med*. 2015;372(16):1500-1509. PRIME[+].

Evolocumab (OSLER-1 and OSLER-2) Safety Analysis

	Evolocumab + Standard of Care (n = 2,976)	Standard of Care Alone (n = 1,489)
SAEs	**222 (7.5%)**	**111 (7.5%)**
AEs leading to discontinuation of evolocumab	**71 (2.4%)**	**NA**
Muscle-related	**190 (6.4%)**	**90 (6.0%)**
Injection-site reaction	**129 (4.3%)**	**NA**
Neurocognitive event	**27 (0.9%)**	**4 (0.3)**

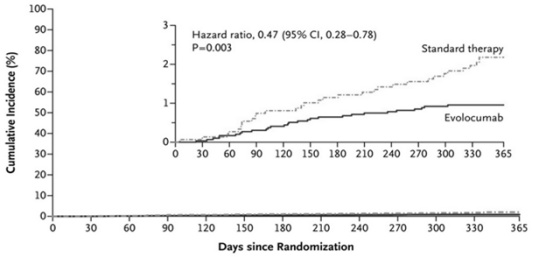
Sabatine MS, et al. *N Engl J Med*. 2015;372(16):1500-1509. PRIME[+].

Evolocumab (OSLER-1 and OSLER-2) Patient Incidence of Cardiovascular Clinical Events

Endpoint	Evolocumab + Standard Therapy (n = 2,976)	Standard Therapy Alone (n = 1,489)	HR (95% CI)
All CV events	**29 (0.95%)**	**31 (2.18%)**	**0.47 (0.28–0.78)**
Death	**4 (0.14%)**	**6 (0.41%)**	**0.33 (0.09–1.18)**
Coronary events (MI, hospitalization for unstable angina, coronary revascularization)	**22 (0.75%)**	**18 (1.30%)**	**0.61 (0.33–1.14)**
Cerebrovascular events (stroke or TIA)	**4 (0.14%)**	**7 (0.47%)**	**0.29 (0.08–0.98)**
Heart failure requiring hospitalization	**1 (0.03%)**	**1 (0.07%)**	**0.52 (0.03–8.30)**

Sabatine MS, et al. *N Engl J Med*. 2015;372(16):1500-1509. PRIME[+].

Evolocumab (OSLER-1 and OSLER-2) Cumulative Incidence of Cardiovascular Events



No. at Risk													
Standard therapy	1489	1486	1481	1473	1467	1463	1458	1454	1447	1438	1428	1361	407
Evolocumab	2976	2970	2962	2949	2938	2930	2920	2910	2901	2885	2871	2778	843

Sabatine MS, et al. *N Engl J Med*. 2015;372(16):1500-1509. PRIME[+].

LDL-C reduction with PCSK9 inhibitors

- Long-term effects of very low levels of LDL-C induced by PCSK9 inhibitors are unknown
- Effect on cardiovascular morbidity and mortality has not been determined.
- Potential for immunogenicity
- Safety and effectiveness not established in pediatric patients with primary hyperlipidemia or HeFH

LDL-C = low density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia

LDL-C reduction a reliable surrogate for cardiovascular outcomes?

- Statin approvals based on the LDL cholesterol surrogate (1987)
- Ezetimibe approval based on LDL cholesterol surrogate (2002)
- Nonstatin trials did not support correlation
  - ILLUMINATE study
  - HPS2-THRIVE

What Can We Learn from IMPROVE-IT?

Ezetimibe/Simvastatin vs Simvastatin

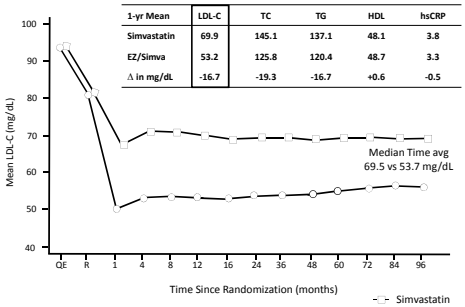
IMPROVE-IT: Ezetimibe/Simvastatin vs Simvastatin

- Large scale (N = 18,144) RCT of high-risk post-ACS patients
  - Intervention: Ezetimibe 10 mg added to simvastatin 40 mg
  - Comparator: Simvastatin 40 mg
  - Simvastatin dose uptitrated to 80 mg in patients with LDL-C > 79 mg/dL
    - 27% in simvastatin group and 6% in ezetimibe/simvastatin group
- Primary endpoint:
  - Composite of cardiovascular death, MI, unstable angina requiring hospitaliziation, coronary revascularization, or stroke
- Study took 9 years; follow-up was 7 years

ACS = acute coronary syndrome.
Cannon CP, et al. N Engl J Med 2015;372(25):2387-2397. PRIME*.

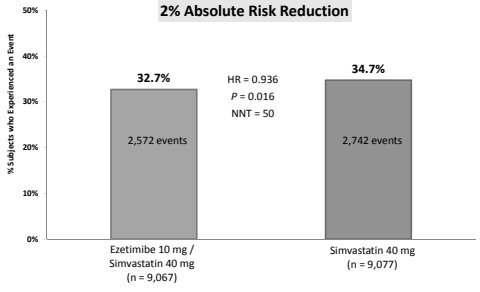
IMPROVE-IT: LDL-C and Lipid Changes

1-yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simvastatin	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



TC = total cholesterol; TG = triglycerides; hsCRP = high sensitivity C-reactive protein.
Cannon CP, et al. N Engl J Med 2015;372(25):2387-2397. PRIME*.

IMPROVE-IT: Results for Primary Endpoint*



*The primary composite endpoint was CV death, nonfatal myocardial infarction (MI), nonfatal stroke, rehospitalization for unstable angina (UA), and coronary revascularization (≥ 30 days postrandomization).
Cannon CP, et al. N Engl J Med 2015;372(25):2387-2397. PRIME*.

IMPROVE-IT: Individual Primary and Secondary Endpoints (7-year event rates)

Clinical Outcomes	Simvastatin n = 9,077 (%)	Ezetimibe/Simvastatin n = 9,067 (%)	*P* Value
All-cause death	15.3	15.4	0.782
MI	**14.8**	**13.1**	**0.002**
Stroke	**4.8**	**4.2**	**0.052**
Ischemic stroke	4.1	3.4	0.008
Unstable angina	1.9	2.1	0.618
Coronary revascularization	23.4	21.8	0.107

Cannon CP, et al. N Engl J Med 2015;372(25):2387-2397. PRIME*.

Key Takeaways from IMPROVE-IT

- Addition of a nonstatin (ezetimibe) to a moderate dose statin may lower cardiovascular event risk
- Reaffirms "lower is better" with proven risk-reducing therapies
- Confirms safety profile of ezetimibe
  - No differences observed in cancer or muscle, or gallbladder-related events
- Questions remain:
  - What is the optimal LDL?
  - How low to go?
  - Should guidelines be changed?

Cannon CP, et al. N Engl J Med 2015;372(25):2387-2397. PRIME[+].

Patient Case #1

- Man followed in lipid clinic for multiple decades
  - PMH: HeFH, known CAD
  - FH: 2 brothers dying from cardiovascular causes in their 20s.
  - SH: highly motivated, getting lots of exercise, trying to eat the right foods, taking 4 lipid-lowering medications (maximum statin therapy as well as other LDL-lowering medications)
- Despite that his LDL-C level is 150 mg/dL

Would you consider a PCSK-9 inhibitor in this patient?

Patient Case #2

- 40 YO Male
  - LDL of 110 mg/dL after maximally tolerated statin
  - Recurrent CV events with multiple stents

Would you consider a PCSK-9 inhibitor in this patient?

PCSK9 inhibitors: Sticker Shock

- Evolocumab costs $14,100 per year
- Alirocumab costs $14,600 per year
- In Europe, PCSK9 inhibitors cost ~ $6,800 USD per year in the United Kingdom
- Every statin is available as a generic medication at a fraction of that cost
  - According to ICER, the PCSK9 inhibitor price would need to come down to $2100 per year to be cost-effective in FH patients, and to approximately $2,500 per year in the secondary-prevention setting

Institute for Clinical and Economic Review. PCSK9 inhibitors for treatment of high cholesterol: effectiveness, value, and value-based price benchmarks draft report. Published September 8, 2015

Statin Intolerance

- Prevalence of statin-associated muscle symptoms ranges from 7% to 29%
- In a large retrospective cohort study, 6579 of 11,124 patients who discontinued a statin due to adverse effects were rechallenged, with 92% success in restoring therapy
- Try multiple statins before labeling statin-intolerant and considering a $14,000 alternative

Key Points

- Establishing improved cardiovascular outcomes is key.
- Ongoing trials are necessary for PCSK 9 inhibitors.
- PCSK9 inhibitors are not for patients simply reluctant to take a statin.
- PCSK9 inhibitors are reserved for patients with "high" LDL cholesterol levels despite maximal therapy with statins and ezetimibe.

QUESTIONS

Thank You

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REFERENCES

- Mozaffarian D, et al. *Circulation*. 2015; 131(4):e29-322; CDC. Heart Disease Facts. www.cdc.gov/heartdisease/facts.htm. Accessed 3/24/15.
- Go AS, et al. *Circulation*. 2014;129(3):E28-E292; Rosenson RS, et al. *J Clin Lipidol*. 2014;8(3 Suppl):S58-S71.
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- Boekholdt SM, et al. *J Am Coll Cardiol.* 2014;64(5):485-494.
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- FDA News Release. FDA approves Praluent to treat certain patients with high cholesterol. Released July 24, 2015. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455883.htm
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- Cannon CP, et al. N Engl J Med 2015;372(25):2387-2397.
- Institute for Clinical and Economic Review. PCSK9 inhibitors for treatment of high cholesterol: effectiveness, value, and value-based price benchmarks draft report. Published September 8, 2015

Update in COPD Pharmacotherapy: Is New Better?

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Memphis, TN
October 24, 2016

Conflict of Interest

- I have no conflicts of interest to disclose.

Learning Objectives

- Compare and contrast the pharmacological and cost differences with new therapy options for COPD compared to older medications.
- Discuss the evidence-based outcomes of newer pharmacologic options based on clinical trials compared to older medications.
- Explain the role of new agents in the medical management of COPD.

Abbreviations

- **COPD**—chronic obstructive pulmonary disease
- **FEV1**—forced expiratory volume in 1 second
- **R**—randomized
- **DD**—double dummy
- **DB**—double blind
- **PC**—placebo controlled
- **PG**—parallel group
- **CAT**—COPD assessment test
- **mMRC**—modified medical research council dyspnea scale
- **GOLD**—Global Initiative on Chronic Obstructive Lung Disease
- **SABA**—short acting beta agonist
- **SAMA**—short acting muscarinic antagonist
- **LABA**—long-acting beta agonist
- **LAMA**—long-acting muscarinic antagonist
- **ICS**—inhaled corticosteroids
- **QoL**—quality of life
- **AUC**—area under the curve
- **TDI**—transient dyspnea index
- **PIFR**—peak inspiratory flow rate

What is COPD?

A common **preventable** and **treatable** disease

Characterized by persistent airflow limitation that is usually **progressive**

Associated with an enhanced **chronic inflammatory response** in the airways and the lung

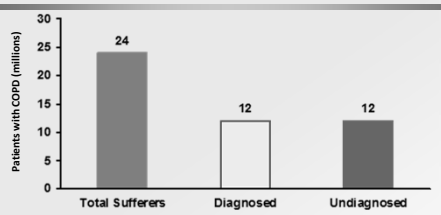
Global Initiative for Chronic Obstructive Lung Disease 2016. http://www.goldcopd.com. Accessed 8/4/16

Epidemiology and Burden of COPD

- 24 million Americans have COPD; half don't know it
- 4th leading cause of death in the world
- 2nd to heart disease as a cause of disability
- Approximately 70% of COPD patients are <65 years and COPD patients under the age of 65 account for:
  - 52% of total hospital outpatient visits for COPD
  - 63% of emergency department visits for COPD
  - 33% of COPD Hospitalizations
- Since 2000, female deaths have exceeded male deaths

Mannino DM. Chest. 2002;121:121S-126S.
AHRQ Pub No. 02-M016, March 2002.
Guarascio AJ et al. Clinicoecon Outcomes Res. 2013;5:235-245.
Mannino DM et al. MMWR 2002;51(SS-6):1-16.

Approximately 24 Million Americans Have COPD; Half Are Undiagnosed



- Patients typically seek medical attention at the moderate stage of COPD
- Since 1987, the prevalence of COPD among women has been significantly higher than that among men

Guarascio AJ, et al. Clinicoecon Outcomes Res. 2013;5:235-245
Mannino DM, et al. MMWR Surveill Summ. 2002;51(6):1-16.
American Lung Association. Trends in chronic bronchitis and emphysema: morbidity and mortality. February 2010. www.lungusa.org. Accessed July 2016..

Significant Burden Associated With Managing COPD

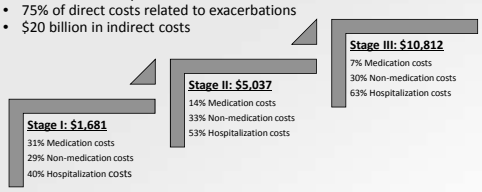
- Each year due to COPD, there are approximately:
  - 16.3 million office visits
  - 672,000 hospitalizations
- More than 22% of Medicare patients hospitalized for COPD in 2003–2004 were readmitted within 30 days of discharge; 36% of these readmissions were for COPD

Jencks SF et al. N Engl J Med. 2009;360:1418-1428.

Cost Based on Disease Progression

Total Cost per patient per year

- Annual COPD cost in 2010 was estimated at $50 billion
  - Direct medical expenditures estimated $30 billion
  - 75% of direct costs related to exacerbations
  - $20 billion in indirect costs



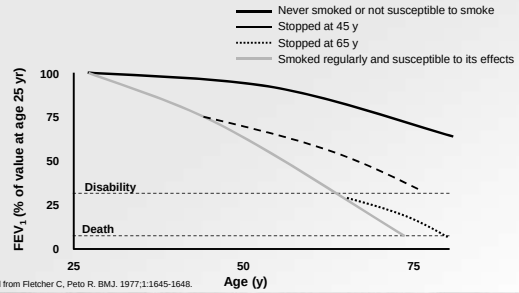
Guarascio AJ et al. Clinicoecon Outcomes Res. 2013;5:235-245

The Major Risk Factor for COPD

- Cigarette smoking is the most important risk factor for COPD worldwide
- About 15% of smokers will develop COPD but the majority of smokers will develop loss of lung function
- Recommendation from the GOLD Guidelines:
  - Any current or former smoker over age 40 or never a smoker with a family history of COPD who complains of dyspnea, chronic cough, or chronic sputum production should seek testing for COPD with spirometry

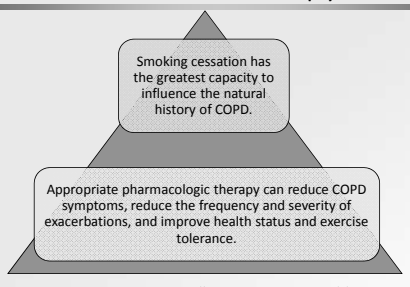
Global Initiative for Chronic Obstructive Lung Disease. www.goldcopd.com. Accessed July 2016.
American Lung Association. www.lungusa.org/lung-disease/copd/resources/facts-figures/COPD-Fact-Sheet.html . Accessed July 2016.

Age-Related Decline in FEV_1 in Smokers



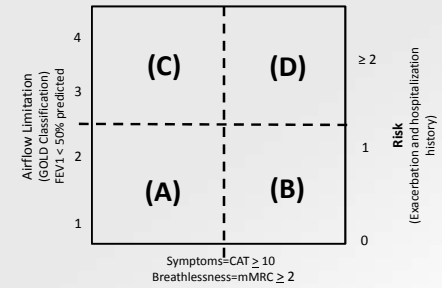
Adapted from Fletcher C, Peto R. BMJ. 1977;1:1645-1648.

Goals of Therapy



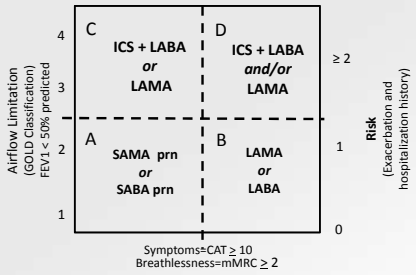
Global Initiative for Chronic Obstructive Lung Disease 2016. http://www.goldcopd.com. Accessed 8/4/16

Combined Assessment of COPD



Adapted from Global Initiative for Chronic Obstructive Lung Disease 2016. http://www.goldcopd.com. Accessed 8/4/16

COPD Assessment and Therapeutic Options



Adapted from Global Initiative for Chronic Obstructive Lung Disease 2016. http://www.goldcopd.com. Accessed 8/4/16

Short-acting bronchodilators

SABA vs SAMA

- Ipratropium vs Albuterol
  - Mild ↑ FEV1 and FVC
  - ↓ oral corticosteroids
  - Improve QoL scores
  - ↓ medication related adverse events
- **NO** recommendation of one over the other

Appleton S, et al. Cochrane Database of Systemic Reviews. 2006.
Friedman, et al. Chest. 1999;115:635-641

SABA/SAMA combination

- ↑ FEV1 and FVC
- Similar safety profile
- Similar symptom and QoL scores
- ↓ oral corticosteroids
- ↓ exacerbations

Rennard et al. Chest. 1996;110:62-70
Tashkin D, et al. Am J Med. 1996;100:62S-69S.

Long-acting bronchodilators

Long-Acting Beta Agonist

- Salmeterol, Formoterol, Arformoterol
- Q 12 hr dosing

- **Vs. SABA**
  - Improve compliance
  - ↑ FEV1
  - ↓ symptoms
  - ↓ exacerbations
  - ↑ QoL

Mahler DA, et al. Chest. 1999;115:957-965.
Rennard SI, et al. Am J Respir Crit Care Med. 2001;163:1087-1092

Long-Acting Muscarinic Antagonist

- Tiotropium
- Qday dosing

- **Vs. active comparator**
  - UPLIFT Trial
  - ↑ Lung function and QoL
  - ↓ Dyspnea, exacerbations, and hospital days

Brusasco V, et al. Thorax. 2003;58:399-404.
Tashkin D, et al. N Engl J Med. 2008;359:1543-54

Inhaled Corticosteroids

- None have an indication for COPD as monotherapy
- This isn't asthma!

	Copenhagen	Euroscope	Lung Health II	Isolde
Pts / Length (mo)	290 / 36	912 / 36	1116 / 40	751 / 36
Med	Budesonide	Budesonide	Triamcinolone	Fluticasone
Baseline FEV1 % predicted	86%	77%	64%	46%
Exacerbations	↔	↔	↔	↓
FEV1 response	None	None	None	↑
FEV1 Decline	↔	↔	↔	↔

Vestbo et al. Lancet. 1999;35:1819.
Pauwels et al. N Engl J Med. 1999;340:1948.
Anthonisen et al. N Engl J Med. 2000;343:1902.
Burge et al. BMJ. 2000;320:1297.

ICS/LABA combination

TORCH study

Combination therapy vs LABA
- ↑ FEV1
- ↑ QoL
- ↓ exacerbations
- ↑ pneumonia

Type of trial	• R,DB,PC of 6112 pts • Baseline FEV1 % predicted-44%
Intervention	• Placebo • Fluticasone • Salmeterol • Fluticasone/Salmeterol combo
Primary Endpoint	Mortality - ↓ 2.6% vs placebo (p=NS)

Secondary Endpoints	• Exacerbations
	  • 25% ↓ vs placebo (NNT=4)
	  • ↓ exacerbations vs. all Tx arm (p<0.05)
	• Hospitalizations
	  • 17% ↓ vs placebo (p<0.03)
	• FEV1
	  • ↑ FEV1 vs each arm (p<0.05)
	• Pneumonia
	  • ↑ risk by 7.3% vs placebo (NNH=14)

Calverley PMA, et al. N Engl J Med 2007;356:775-89.

How do we keep up?!!!

Pre-1990
- Albuterol
- Ipratropium

1990-2010
- Tiotropium
- Inhaled Steroids
- Salmeterol or Formoterol Combos

2011--Present

11 NEW FDA meds since 2011

- **PDE4 inhibitors**
- **Ultra LABA**
- **Once daily ICS/LABA combo**
- **Four new LAMA**
- **Four new LABA/LAMA combos**

New COPD Products

Phosphodiesterase 4 (PDE-4) inhibitor
Roflumilast—2011

Long-acting beta agonist (LABA)
Indacaterol—2011
Olodaterol—2014

Long-acting muscarinic antagonist (LAMA)
Aclidinium—2012
Umeclidinium—2014
Glycopyrrolate--2015

Inhaled Corticosteroid/LABA Combination
Fluticasone/vilanterol—2013

LABA/LAMA Combination
Umeclidinium/vilanterol—2013
Glycopyrrolate/indacaterol—2015
Tiotropium/olodaterol—2015
Glycopyrrolate/formoterol—2016

Phosphodiesterase 4 Inhibitors

Roflumilast (Daliresp®)

Medication characteristics	
MOA	Selectively inhibits phosphodiesterase-4 (PDE4) → accumulation of cyclic AMP (cAMP) within inflammatory and structural cells
Dose	500 mcg once daily
Pharmacokinetics	• **Bioavailability:** ~ 80% • **Metabolism:** CYP3A4 and CYP1A2 to active metabolite • **T1/2:** 17 hours; 30 hours active metabolite • **Time to peak:** ~ 1 hours (delayed by food); Active metabolite ~ 8 hours • **Excretion:** Urine
Contraindications	Moderate or severe hepatic impairment
Common side effects	Weight loss, decrease appetite, diarrhea, nausea, backache, dizziness, headache, insomnia
Formulation	Oral tablet
Cost	$354.14 AWP, package size 30s each
Place in therapy	GOLD C and D FEV1 < 50% and ≥ 2 exacerbations/yr

http://www.azpicentral.com/daliresp/pi_daliresp.pdf. Accessed 8/12/16

Roflumilast vs Placebo

- Replicate, R,DB, PC, PG x 56 weeks
- Patients:
  - Age > 40 with exacerbation within the past year
  - FEV1 % predicted < 50%
  - n=3091

Trial	Outcomes	Roflumilast	Placebo	Change	p Value
M2-124	Δ in Trough FEV1 at 56wks (mL)	45	8	37	p<0.0003
	Exacerbations per patient/year	1.08	1.27	15%	p<0.0278
M2-125	Δ in Trough FEV1 at 56wks (mL)	33	-25	58	p<0.05
	Exacerbations per patient/yr	1.2	1.5	18%	p<0.05

Calverley PM et al. Lancet. 2009 Aug 29;374(9691):685-94.

Long-acting Beta Agonists

Indacaterol (Arcapta™ Neohaler™)

Medication characteristics	
MOA	Ultra-LABA
Dose	75 mcg inhaled once daily
Pharmacokinetics	**Metabolism:** CYP3A4, CYP2D6, and CYP1A1 **T1/2:** 40-56 hours **Time to peak:** ~15 minutes **Excretion:** Feces and urine
Contraindications	Hypersensitivity to indacaterol or any component of the formulation
Common side effects	Cough, headache, nausea, nasopharyngitis, oropharyngeal pain
Formulation	Capsule, inhalation - PIFR of 52-133 L/min
Cost	$256.33 AWP, package side 30s each
Place in therapy	Monotherapy GOLD B Combination therapy in GOLD C and D

https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/arcapta.pdf. Accessed 8/13/16

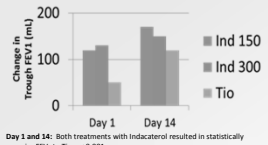
Indacaterol vs Placebo or Twice Daily LABA

Clinical Trial Data		
	Indacaterol vs Placebo	**Indacaterol vs BID LABA**
Type of trial	Six randomized, double blinded **placebo** controlled trial	Meta-analysis of 4 studies Indacaterol daily **vs BID LABA's** for > 24 wks
Patients	5,474 patients with COPD • ≥ 40 years of age • History of smoking at least 10 pack years • FEV_1 of at least 30% and less than 80% of predicted	4708 patients with COPD • ≥ 40 years of age • History of smoking at least 10 pack years • FEV_1 of at least 30% and less than 80% of predicted
Outcomes	• Significantly greater 24-hour post-dose trough FEV1 vs placebo • ↑ Trough FEV1 by > 120 mL (p<0.05) • Reduced exacerbations by 31% vs placebo	Improved: • Trough FEV1 73 mL (p<0.05) • Dyspnea 0.54 via TDI (p<0.05) No difference in: • Peak FEV1 • QoL scores • Exacerbations or Mortality • Adverse effects

Kerwin EM et al. Clin Ther. 2011;33:1974.
Wedzicha JA et al. Respir Med. 2015 Jan;109(1):105-11.
Geake JB et al. Cochrane Database of Systematic Reviews 2015, Issue 1. Art. No.: CD010139

Indacaterol vs Tiotropium

LABA vs LAMA – 14 Days	
Type of trial	Randomized, DB, PC, DD, crossover (n=169)
Intervention	Indacaterol vs Tiotropium
Outcomes	Indacaterol was at least as effective as tiotropium with a faster onset



Day 1 and 14: Both treatments with Indacaterol resulted in statistically superior FEV_1 to Tio p < 0.001

LABA vs LAMA – 6 Month Duration	
Type of trial	R, PG study
Patients	1422 pts in GOLD A or B
Intervention	Indacaterol vs Tiotropium
Outcomes	↑FEV_1 30 mL; ↓ rescue SABA; dyspnea↑QoL (All p<0.05)

Vogelmeier et al. Respir Res. 2010;5(11):135.
Mahler DA et al. Respir Med. 2015; 109(8);1031-1039.

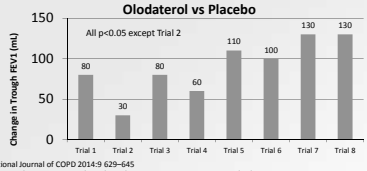
Olodaterol (Striverdi™ Respimat®)

Medication characteristics	
MOA	Long-acting Beta Agonist
Dose	Two inhalations once daily (2.5 mcg/actuation)
Pharmacokinetics	**Bioavailability:** 30% **Metabolism:** Direct glucuronidation and O-demethylation **t1/2:** 7.5 hours **Time to peak:** 10-20 minutes **Excretion:** Feces and urine
Contraindications	Patients with asthma not taking a long-term controller medication
Common side effects	nasopharyngitis, skin rash, UTI, back pain, bronchitis
Formulation	Aerosol Solution, inhalation
Cost	$155.70 AWP
Place in therapy	Monotherapy GOLD B Combination therapy in GOLD C and D

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/203108s000lbl.pdf. Accessed 8/13/16

Olodaterol vs Placebo

Olodaterol vs Placebo	
Type of trial	• 8 confirmatory trials vs placebo • Replicate, R, DB, PC
Patients	3,533 COPD patients • GOLD class 2 and 3 • Age > 40 yrs • 10 yr history of smoking



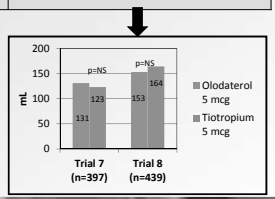
Ferguson GT et al. International Journal of COPD 2014:9 629–645
https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/203108s000lbl.pdf. Accessed 8/13/16

Olodaterol vs Formoterol or Tiotropium

	Olodaterol vs Formoterol	Olodaterol vs Tiotropium
Type of Trial	Two R, DB, DD trials	Two R, DB trials
Intervention	vs Formoterol 12mcg BID	vs Tiotropium
Outcomes	Change in Trough FEV1 from baseline Similar profiles for all other metrics	Change in $FEV1\ AUC_{12-24}$

	Olodaterol	Formoterol
Trial 5 (n=906)	78 mL*	54 mL*
Trial 6 (n=937)	53 mL*	42 mL*

*p<0.05 vs placebo



Koch A. et al. Int J COPD 2014:9 697–714.
Lange P et al. J Pulm Respir Med 2014;4: 196

Long-acting Antimuscarinc Antagonists

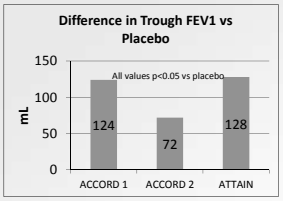
Aclidinium (Tudorza® Pressair®)

Medication characteristics	
MOA	Long-acting muscarinic antagonist
Dose	1 inhalation twice daily (400 mcg/actuation)
Pharmacokinetics	**Metabolism:** Hydrolysis **t1/2:** 5-8 hours **Time to peak:** within 10 minutes **Excretion:** Urine
Contraindications	Severe hypersensitivity to milk proteins, aclidinium, or any of the excipients
Common side effects	Headache, diarrhea, nasopharyngitis, cough
Formulation	Aerosol power breath activated, inhalation Minimal PIFR of 35 L/min
Cost	$301.10 AWP
Place in therapy	Monotherapy GOLD B Combination therapy in GOLD C prior to steroids

http://www.azpicentral.com/tudorza/tudorza_pi.pdf. Accessed 8/13/16

Aclidinium vs Placebo

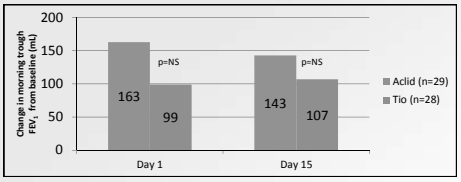
Aclidinium study	
Type of Trial	Randomized, double blind, placebo controlled
Patients	1,933 subjects with COPD • ≥ 40 years of age • History of smoking at least 10 pack years • FEV_1 of at least 30% and less than 80% predicted FEV_1/FVC of less than 0.7
Outcomes	• Improvement in FEV1 • ↓ rescue SABA use



Kerwin EM et al. COPD. 2012;9:90-101.
Jones PW et al. Eur Respir J. 2012;40:830-836.
Rennard SI et al. Clin Drug Investig. 2013;33:893-904.

Aclidinium vs Tiotropium

Aclidinium vs Active Comparator	
Type of Trial	Randomized, DB, DD, PC, crossover
Intervention	Aclidinium BID, Tio QD, placebo 15 days
Outcomes	Improvements in 24-h bronchodilation were comparable to Tiotropium



Fuhr et al. CHEST. 2012; 141(3):745-752

Umeclidinium (Incruse® Ellipta®)

Medication characteristics	
MOA	Long-acting muscarinic antagonist
Dose	1 inhalation once daily (62.5 mcg/actuation)
Pharmacokinetics	**Metabolism:** CYP2D6 **t1/2:** 11 hours **Time to peak:** 5 – 15 minutes **Excretion:** Feces and urine
Contraindications	Severe hypersensitivity to milk proteins or any component
Common side effects	Tachycardia, nasopharyngitis, upper respiratory tract infection, cough
Formulation	Aerosol power breath activated, inhalation Minimal PIFR of 35 L/min
Cost	$252.60 AWP
Place in therapy	Monotherapy GOLD B Combination therapy in GOLD C prior to steroids

https://www.gsksource.com/Prescribing_Information/Incruse_Ellipta/pdf/INCRUSE-ELLIPTA-PI-PIL.PDF. Accessed 8/13/16

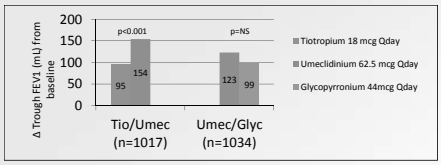
Umeclidinium vs Placebo

Umeclidinium studies	
Type of trial	Randomized, double-blind, placebo controlled, parallel group trials • 24-week placebo controlled trial • 12 week placebo controlled trial
Patients	n=1,738 pts • 10 yr history of smoking • FEV1 < 70% predicted • FEV1/FVC < 0.70
Outcomes	• Mean ↑ in Trough FEV1 of 127 mL (p<0.05) • QoL scores improved 30%

Trivedi R et al. Eur Respir J. 2014;43:72–81
https://www.gsksource.com/Prescribing_Information/Incruse_Ellipta/pdf/INCRUSE-ELLIPTA-PI-PIL.PDF. Accessed 8/13/16

Umeclidinium vs other LAMA's

	Umeclidinium vs Tiotropium	Umeclidinium vs Glycopyrronium
Type of trial	R, B, DD, PG x 12 wks	R, Open label, PG x 12 wks
Patients	• Age > 40 • GOLD 2 and 3 with mMRC ≥ 2	• Age > 40 • GOLD 2 and 3 with mMRC ≥ 2



Feldman et al. Int J Chron Obstruct Pulmon Dis. 2016. 7;11:719-30
https://clinicaltrials.gov/ct2/show/study/NCT02236611?sect=X70156. Accessed 8/11/16

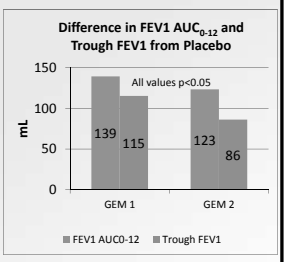
Glycopyrrolate (Seebri™ Neohaler®)

Medication characteristics	
MOA	Long-acting muscarinic antagonist
Dose	1 inhalation twice daily (15.6 mcg/actuation)
Pharmacokinetics	**Metabolism:** multiple CYP enzymes **t1/2:** 33-43 hours **Time to peak:** 5 minutes **Excretion:** Feces and urine
Contraindications	Hypersensitivity to glycopyrrolate or to any of the ingredients
Common side effects	Sinusitis, nasopharyngitis, upper respiratory tract infection, oropharyngeal pain, urinary tract infection
Formulation	Capsule, inhalation PIFR of 52-133 L/min
Cost	$ 297.80 AWP
Place in therapy	Monotherapy GOLD B Combination therapy in GOLD C prior to steroids

https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/seebri.pdf. Accessed 8/13/16.

Glycopyrrolate vs Placebo

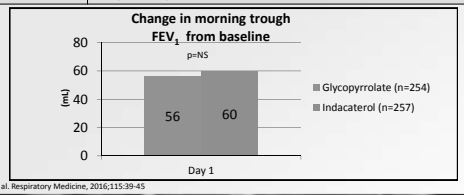
Glycopyrrolate study	
Type of Trial	Randomized, double blind, placebo controlled, parallel group x 12 wks
Patients	867 subjects with COPD • ≥ 40 years of age • History of smoking at least 10 pack years • FEV_1 of at least 30% and less than 80% predicted • mMRC ≥ 2
Outcomes	• Improvement in FEV1 • ↓ rescue SABA use • ↑ QoL and dyspnea scores



LaForce C et al. Int J of Chron Obst Pulmon Dis. 2016 Jun 8;11:1233-43
Kerwin E et al. Chronic Obstr Pulm Dis (Miami). 2016; 3(2): 549-559

Glycopyrrolate vs Indacaterol

Aclidinium vs Active Comparator	
Type of Trial	Randomized, DB, PC study x 52 weeks (GEM 3 Study)
Intervention	Glycopyrrolate 15.6 mcg INH BID vs Indacaterol 75 mcg INH daily
Outcomes	Improvements in 24-h bronchodilation were comparable Indacaterol reduced SABA use vs Glycopyrrolate (p<0.05) Safety was comparable



Mahler DA et al. Respiratory Medicine, 2016;115:39-45

Inhaled Corticosteroid/Long-acting Beta Agonist Combination

Fluticasone/vilanterol (Breo® Ellipta®)

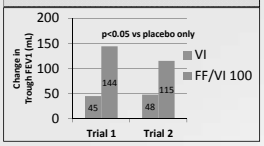
Medication characteristics	
MOA	Inhaled corticosteroid and long-acting beta agonist combination
Dose	1 inhalation once daily (100mcg/25mcg per actuation)
Pharmacokinetics	**Metabolism:** CYP3A4 **t1/2:** ~24 hours **Time to peak:** Fluticasone < 1 hr/ Vilanterol 10 min **Excretion:** Feces and Urine
Contraindications	Primary treatment of acute asthma or COPD exacerbation Severe hypersensitivity to milk proteins or any ingredients
Common side effects	Cough, headache, nausea, nasopharyngitis, oropharyngeal pain
Formulation	Aerosol power breath activated, inhalation PIFR 43-81 L/min
Cost	$267.00 AWP, package size 60 blisters
Place in therapy	GOLD C (potentially after LABA/LAMA combo)

https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Anoro_Ellipta/pdf/ANORO-ELLIPTA-PI-MG.PDF. Accessed 8/13/16

Fluticasone/vilanterol Lung Function and Exacerbation Trials

Lung Function Studies

- Replicate, R DB, PC, PG, 24 wks
- n=2,254
- Mean FEV1 % predicted is 48%



Martinez FJ et al. Respir Med. 2013; 107: S50-S59
Kerwin EM et al. Respir Med. 2013;107(4):560-569

Exacerbation Studies

- Replicate, R, DB, PG, 52 wks
- n=3,255
- Mean FEV1% predicted is 45%

Annual Rate of Exacerbations			
	FF/VI	Vilanterol	% Change (*p<0.05)
Trial 3 (n=1622)	0.90	1.14	↓21%*
Trial 4 (n=1633)	0.70	1.05	↓34%

Dransfield MT et al. Lancet Resp Med. 2013;1(3):210-223.

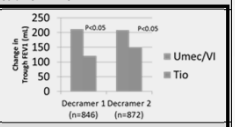
Long-acting Beta Agonist/Long-acting Muscarinic Antagonist Combination

Umeclidinium/vilanterol (Anoro® Ellipta®)

Medication characteristics	
MOA	Long-acting muscarinic antagonist and long-acting beta agonist combination
Dose	1 inhalation once daily (62.5 mcg/25 mcg per actuation)
Pharmacokinetics	**Metabolism:** CYP2D6 (umec) and CYP3A4 (vil) **t1/2:** 11 hours **Time to peak:** **Excretion:** Urine and feces
Contraindications	Severe hypersensitivity to milk proteins or any ingredients
Common side effects	Diarrhea, pharyngitis, chest pain
Formulation	Aerosol power breath activated, inhalation PIFR 43-81 L/min
Cost	$315.70 AWP, package size 60 blisters
Place in therapy	GOLD B after failure of monotherapy or GOLD C

https://www.gsksource.com/Prescribing_Information/Anoro_Ellipta/pdf/ANORO-ELLIPTA-PI-MG.PDF. Accessed 8/13/16

Umeclidinium/Vilanterol Clinical Trials

	Donohue et al	Decramer et al
Type of trial	Randomized, DB, PC, PG over 24 wks	Replicate, Randomized, blind, DD, PG, 24 wks
Intervention	Combo, UMEC 62.5 mcg, VI 25 mcg, placebo	Umec/VI vs Tiotropium
Patients	n=1,532 mMRC ≥ 2	Decramer 1- n=846 Decramer 2- n=872
Outcomes	• FEV_1 +52 mL versus 95 mL and 167 mL respectively (p<0.05) • Dyspnea and QoL similar in all groups • ↓ exacerbations	 No difference for QoL, symptoms, and exacerbations

Cohen JS et al. Int J COPD. 2016;11:785-797.
Donohue JF et al. Respir Med. 2013;107(10):1538-1546.
Decramer M et al. Lancet Respir Med. 2014;2(6):472-486

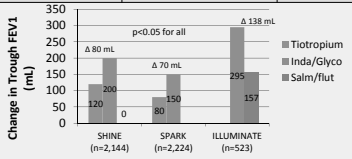
Indacaterol/Glycopyrrolate (Utibron™ Neohaler®)

Medication characteristics	
MOA	Long-acting muscarinic antagonist and long-acting beta agonist combination
Dose	1 capsule inhaled twice daily (27.5 mcg/15.6 mcg per actuation)
Pharmacokinetics	**Metabolism:** multiple CYP enzymes **t1/2:** ~53 hours **Time to peak:** 5-15 minutes **Excretion:** Feces and Urine
Contraindications	Asthma without use of a long-term controller medication History of known hypersensitivity to indacaterol, glycopyrrolate.
Common side effects	Nasopharyngitis, Rhinitis, hypertension, headache, diarrhea, GERD
Formulation	Capsule, inhalation PIFR of 52-133 L/min
Cost	$297.80 AWP
Place in therapy	GOLD B after failure of monotherapy or GOLD C

https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/utibron.pdf. Accessed 8/13/16

Indacaterol/Glycopyrrolate vs Active Comparator

	SHINE	SPARK	ILLUMINATE
Type of trial	R, DB, PC, PG	R, DB, PG	R, DB, DD
Intervention	• Inda/Gly vs Tiotriopium • 26 wks	• Inda/Gly vs Tiotriopium • 64 wks	• Inda/Gly vs Salmeterol/fluticasone • 26 wks
Patients	FEV1 % Predicted of 30-80%	FEV1 < 50% with ≥ 1 exacerbation	FEV1 % Predicted of 30-80%



Take Home: Improvements in FEV1, QoL, symptoms, rescue SABA, and exacerbations
***NOTE:** ALL studies conducted with higher than FDA approved dose

Cohen JS et al. Int J COPD. 2016;11:785-797.
Wedricha J et al. Lancet Respir Med. 2013;1:199-209.
Bateman ED et al. Eur Respir J 2013;42:1484-1494.
Vogelmeier CF et al. Lancet Respir Med. 2013;1:51-60.

FLAME Study

Indacaterol/Glycopyrrolate vs Salmeterol/Fluticasone			
Type of trial	R, DB, DD, PG, non-inferiority, multi-center, 52 wks		
Intervention	Indacaterol/Glycopyrrolate 110/50 mcg Qday Salmeterol/Fluticasone 50/250 mcg bid		
Patients	n=3,362 Age > 40 FEV1 % predicted 25-60% mMRC ≥ 2		
	Indacaterol/ Glycopyrrolate	Salmeterol/ Fluticasone	p value
Primary Outcome Exacerbations/yr	3.59	4.03	0.003
Secondary Outcomes			
Time to first exacerbation	71 days	51 days	<0.001
Incidence of pneumonia	3.2%	4.8%	0.02
Change in Trough FEV1 from baseline	15 mL	-48 mL	<0.001

Wedzicha JA et al. N Engl J Med 2016;374:2222-34.

Tiotropium/olodaterol (Stiolto® Respimat®)

Medication characteristics	
MOA	Long-acting muscarinic antagonist and long-acting beta agonist combination
Dose	Two inhalations once daily (2.5 mcg/2.5 mcg per actuation)
Pharmacokinetics	**Metabolism:** multiple CYP enzymes **t1/2:** 25-45 hours **Time to peak:** 5-10 minutes **Excretion:** Feces and Urine
Contraindications	Patients with asthma without a controller medication Hypersensitivity to tiotropium, ipratropium, olodaterol
Common side effects	Nasopharyngitis and cough
Formulation	Aerosol solution, inhalation
Cost	$315.70 AWP
Place in therapy	GOLD B after failure of monotherapy or GOLD C

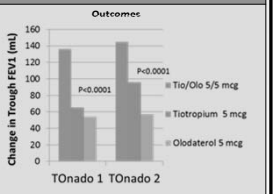
http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Stiolto%20Respimat/stiolto.pdf. Accessed 8/13/16

Tiotropium/Olodaterol vs Individual Components

	TOnado 1 and 2
Type of trial	Randomized, double-blind, parallel group

Intervention	• Treatment groups (daily dose)
	  • T/O 2.5/5 mcg
	  • T/O 5/5 mcg
	  • TIO 2.5 mcg
	  • TIO 5 mcg
	  • OLO 5 mcg
	• 52 weeks

Patients	• 5,163 COPD patients
	  • ≥ 40 yrs old
	  • Smoking history of > 10 pack-years
	  • Moderate to very severe pulmonary impairment



- ↑ FVC and QoL
- ↓ rescue SABA and exacerbations

Buhl R et al. Eur Respir J 2015; 45: 869–871

Tiotropium/Olodaterol vs Salmeterol/Fluticasone

ENERGITO Study			
Type of trial	Randomized , double-blind, double-dummy with four 6 wk treatment arms, each followed by 3 wk washout		
Patients	n=220 pts • 10 yr history of smoking • FEV1/FVC < 0.70 • GOLD Class 2 and 3		
Adjusted Mean FEV1 AUC			
	Tio/Olo 2.5/2.5	Salmeterol/Fluticasone 50/250	Difference *p<0.05
FEV1 AUC (0-12hrs)	317 mL	192 mL	125 mL*
FEV1 AUC (12-24hrs)	172 mL	132 mL	40 mL*
Conclusion	Improved lung function and hyperinflation at all time points		

Beeh KM et al. Int J COPD. 2016;11:193-205

Glycopyrrolate/formoterol (Bevespi Aerosphere™)

Medication characteristics	
MOA	Long-acting muscarinic antagonist and long-acting beta agonist combination
Dose	Two inhalations twice daily (9mcg/4.8 mcg per inhalation)
Pharmacokinetics	**Metabolism:** CYP2D6 and CYP2C **t1/2:** 11.8 hours **Time to peak:** 5-20 minutes **Excretion:** Feces and Urine
Contraindications	Patients with asthma without use of a long-term control medication Hypersensitivity to glycopyrrolate, formoterol, or any component
Common side effects	Nasopharyngitis and cough
Formulation	Aerosol, inhalation
Cost	Not available
Place in therapy	GOLD B after failure of monotherapy or GOLD C

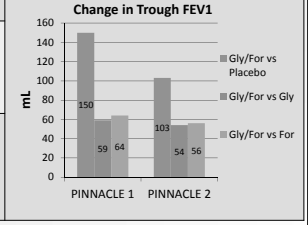
http://www.azpicentral.com/bevespi/bevespi_pi.pdf. Accessed 8/13/16

Glycopyrrolate/formoterol vs Individual Components

PINNACLE 1 and 2	
Type of trial	Replicate, randomized, double-blind, placebo controlled, parallel group

Intervention	• Treatment groups (2 puffs bid)
	  • Gly/For 9/4.8 mcg
	  • Gly 9 mcg
	  • For 4.8 mcg
	  • Placebo
	• 24 weeks

Patients	• 3,699 COPD patients
	  • ≥ 40 yrs old
	  • Smoking history of > 10 pack-years
	  • Moderate to very severe pulmonary impairment



http://www.azpicentral.com/bevespi/bevespi_pi.pdf. Accessed 8/13/16

Too many choices!

So, which agent do we choose?

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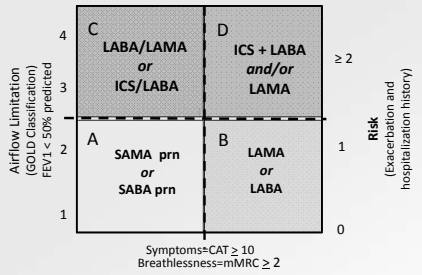
Disease Assessment



Adapted from Global Initiative for Chronic Obstructive Lung Disease 2016. http://www.goldcopd.com. Accessed 8/4/16

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Drug	Formulation	Dosage	Wholesale Cost
Long-Acting Muscarinic Antagonist			
Tiotropium	18 mcg/cap DPI 2.5 mcg/inh ISI	1 inh Qday 2 inh Qday	$315.70
Aclidinium	400 mcg/inh DPI	1 inh bid	$301.10
Glycopyrrolate	15.6 mcg/cap DPI	1 inh bid	$297.80
Umeclidinium	62.5 mcg/inh DPI	1 inh Qday	$252.60
Long-Acting Beta Agonist			
Salmeterol	50 mcg/blister DPI	1 inh bid	$322.60
Formoterol		1 inh bid	$251.00
Indacaterol	75 mcg/cap DPI	1 inh Qday	$213.60
Olodaterol	2.5 mcg/inh ISI	2 inh Qday	$155.70
Long Acting Beta Agonist/Long Acting Muscarinic Antagonist Combo			
Glycopyrrolate/Indacaterol	15.6/27.5 mcg/cap DPI	1 inh bid	$297.80
Tiotropium/Olodaterol	2.5/2.5 mcg/inh ISI	2 inh Qday	$315.70
Umeclidinium/vilanterol	62.5/25 mcg/blister DPI	1 inh Qday	$315.70
Glycopyrrolate/formoterol	9/4.8 mcg/inh MDI	2 inh bid	Not available
Inhaled Corticosteroid/Long-Acting Beta Agonist			
Fluticasone Furoate/Salmeterol	100/25 mcg/blister DPI	1 inh Qday	$267.00

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Delivery Systems

Type	Advantages	Disadvantages
Nebulizer	• Patient coordination not required • Tidal breathing	• Device cleaning required • Expensive • Contamination possible • Not all medication available in solution form
Pressurized metered dose inhaler	• Portable and compact • Treatment time is short • No drug preparation required • Dose-dose reproducibility high	• Coordination of breathing and actuation needed • Necessary hand strength • High pharyngeal deposition
Dry powder inhaler	• Breath-actuated • Less coordination required • Small and portable • Short treatment time • Dose counters	• Requires moderate to high inspiratory flow • Some units are single dose (capsules) • Can result in high pharyngeal deposition
Soft mist inhalers	• Similar to neb but more convenient • Lower pharyngeal deposition • 1/3 the actuation rate of MDI	• High cost • Some coordination required • Limited products

Barrons R et al. Patient Intelligence. 2015;7:53-65.

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Adherence

"Drugs don't work in patients that don't take them"

C. Everett Koop, M.D.

- 60% of COPD pts nonadherent
- Nonadherence leads to:
  - ↑ exacerbations, hospitalizations and mortality
- Reasons:
  - # of meds and dosing frequency contribute significantly
  - Cost

Restrepo RD et al. Int J Chron Obstruct Pulmon Dis. 2008;3(3):371-384.
Agh T et al. Respiration. 2011;82,(4):328–34.
Agh T. http://www.intechopen.com/books/chronic-obstructive-pulmonarydisease-current-concepts-and-practice/adherence-to-therapy-in-chronic-obstructive-pulmonary-disease. Accessed 8/14/16

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Ideal Therapy for COPD

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Update in COPD Pharmacotherapy: Is New Better?

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Methodist University Hospital
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October 24, 2016

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