

Asthma, COPD and CVD: Why is everyone short of breath?

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Speaker disclosure statement

- *I report no financial relationships relevant to this activity*

Learning Objectives

- Define and describe classification systems for asthma and COPD and the related implications for pharmacological treatment and patient management.
- Discuss medications prescribed in the management of asthma and COPD including short and long-acting bronchodilators, corticosteroids, leukotriene modifiers and theophylline, highlighting the clinical considerations in patients with CVD and interactions with medications commonly used to treat CVD.

Abbreviations and Examples

- ICS- Inhaled corticosteroid
 - Beclomethasone, budesonide, ciclesonide, fluticasone, mometasone
- LABA- Long-acting beta2-agonist
 - Formoterol, indacaterol, olodaterol, salmeterol
- LAMA-Long-acting muscarinic antagonist
 - Acclidinium, glycopyrrolate, tiotropium, umeclidinium
- LTRA- Leukotriene receptor antagonist
 - montelukast
- SABA-Short-acting beta2-agonist
 - Albuterol, levalbuterol
- SAMA-Short-acting muscarinic antagonist
 - Ipratropium
- PDE4 inhibitor
 - Roflumilast

Clinical Case

- Ms. K is a 60-year-old current smoker with COPD/asthma overlap syndrome who presents with a persistent cough for the last 2 weeks.
 - States that she is currently utilizing her albuterol nebs inhaler about 4 times a day.
 - Has some mild clear sputum production and no fevers.
 - Denies any significant shortness of breath on her current 2 L of home oxygen.
 - Has not had any exacerbations since she was hospitalized a little over 2 months ago.
 - States she is working on quitting smoking. She smokes ½ ppd.

Clinical Case

- **PMHx:**

Asthma severe persistent

Allergic rhinitis

High IgE

COPD Gold 2, group D

OSA on CPAP

TB (treated in 1985)

Tobacco abuse

HTN

HL

Allergies: ketorolac (severe asthma exacerbation)

Medications

Albuterol MDI 90 mcg 2 inhalations q4h prn

Glycopyrrolate/formoterol 9/4.8 mcg

2 inhalations bid

Mometasone 200 mcg 1 inhalation bid

Fluticasone 50 mcg 2 sprays each nostril daily

Amlodipine 5 mg daily

Clinical Case

- Vitals(Past 5 Vitals):

• Date	Temp(F/C)	BP	Pulse	RR	SPO2	Oxygen	Height(cm)	Weight(kg)	BMI
• 02/13 09:06	31.88	97.0/36.1	161/79	91		95		86.8	
• 01/25 16:23	30.94	97.9/36.6	126/77	89	18	97	167.0	86.3	
• 12/26 09:03	30.94	98.1/36.7	170/89	98		93	167	86.3	
• 12/14 13:25	31.45	98.4/36.9	165/94	93		94	167	87.7	

Clinical Case

- Pfts
 - Moderate obstructive defect with a bronchodilator response
 - Hyperinflation and gas trapping present
- Abs eos 0.3 thous/uL
- IgE 792
- RAST (+) mites, cockroach
- Lipid Panel
 - Total cholesterol 217 Trig 122 HDL 76 LDL 117 Non-HDL 141
- HgbA1c 5.6
- ECG, abnormal
 - Normal sinus rhythm
 - Left ventricular hypertrophy
 - QTc: 429 ms
- ECHO
 - Hyperdynamic left ventricular function
 - LV ejection fraction is visually est >75%
 - Mild concentric left ventricular hypertrophy
 - Aortic valve not well seen
 - PA systolic pressure not assessed due to inadequate degree of tricuspid insufficiency

COPD and CVD

- 2.5 X risk of being diagnosed with CVD
- 2-5X risk
 - Ischemic heart disease
 - Cardiac dysrhythmia
 - Heart failure
 - Significant and independent predictor of all-cause mortality
- Hypertension
 - most common co-morbidity
- CVD
 - independent risk factor for poor outcomes post hospital discharge
- Smoking cigarettes
- Systemic inflammation
- Physical inactivity
- Arrhythmias
- Endothelial dysfunction

Asthma and CVD

- All cause mortality
 - HR 3.28 (95%CI 3.15-3.41) $p < 0.0001$
- Heart failure
 - HR 2.14 (95%CI 2.06-2.22) $p < 0.0001$
- All coronary heart disease
 - HR 1.40 (95%CI 1.35-1.45) $p < 0.0001$
- All cerebrovascular disease
 - HR 1.20 (95%CI 1.15-1.25) $p < 0.0001$
- No use of asthma medications
 - HR 4.25 (95% CI 4.01-4.52) $p < 0.0001$
- Obesity
- Inflammatory markers
 - Hs-CRP
 - IL-6
 - TNF- α
 - IL-8
 - Fibrinogen

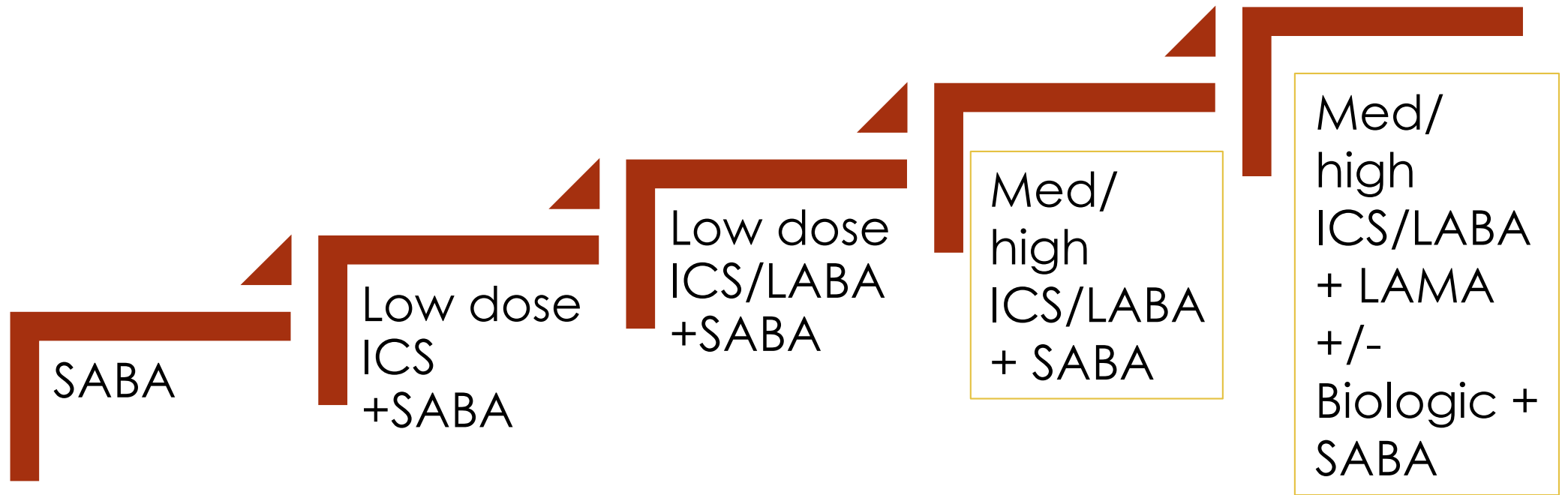
Asthma or COPD or Both

	Asthma	COPD	ACO
Age of onset	Before 20 years	After 40 years	After 40 years
Pattern of symptoms	Days without symptoms Cough at night or early in morning Environmental triggers	Persistent daily symptoms Chronic cough Exertional dyspnea	Persistent daily symptoms Triggers for worsening symptoms
Pulmonary function test	Normal	Obstructive airway with little airway reversibility	Obstructive with airway reversibility
Mainstay treatment	ICS and SABA	LAMA and SABA	ICS/LABA + LAMA and SABA

Initial Controller Treatment for Adults and Adolescents per GINA

Symptom Presentation	Preferred Option (Evidence level)
SABA <2x/month, no waking, no exacerbations in the past year	No controller (D)
SABA use ≥ 2 /week	Low dose ICS (A)
Troublesome asthma symptoms most days, waking due to asthma once a week or more	Medium/high dose ICS (A) or low-dose ICS + LABA (A)
Severely uncontrolled asthma or acute exacerbation	Short course of OCS + high dose ICS (A) or moderate-dose ICS/LABA (D)

Asthma Management



Severity of Airflow Limitation

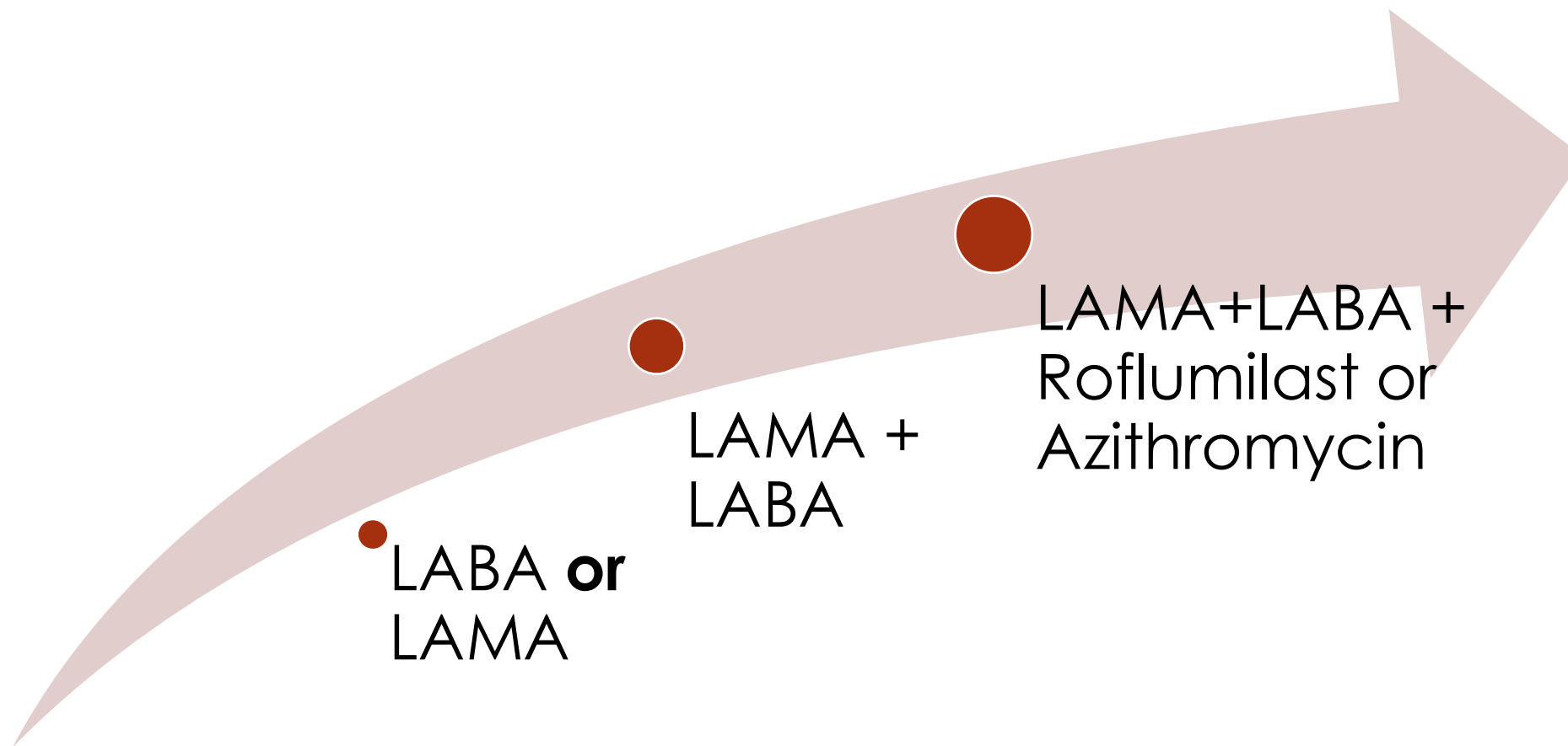
FEV1/Forced Vital Capacity < 70%

GOLD Grade	Post-Bronchodilator FEV1 (% Predicted)
1 Mild	≥ 80%
2 Moderate	50-79
3 Severe	30-49%
4 Very Severe	< 30

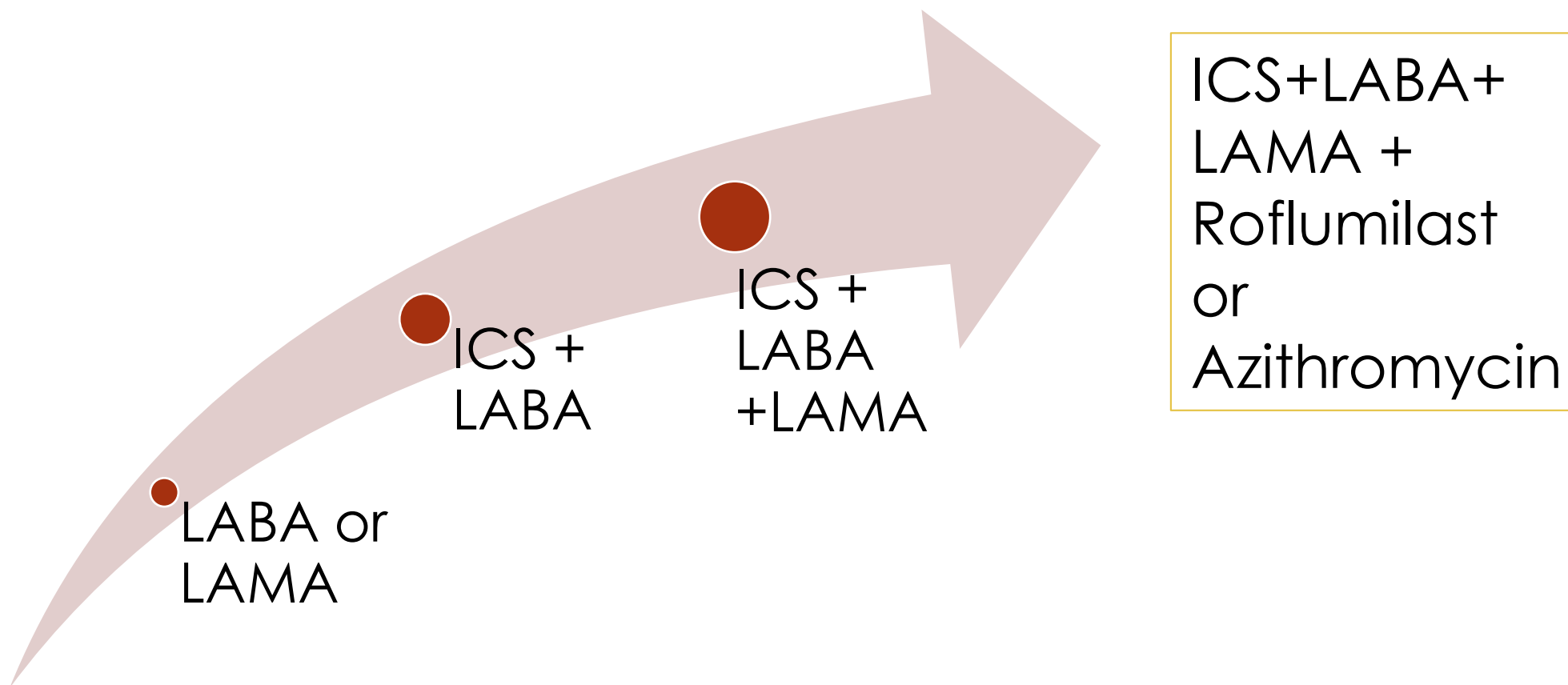
GOLD 2019 Initial Treatment

≥2 outpatient exacerbations (steroid ± antibiotic) or ≥1 COPD hospitalization	<u>Group C</u> LAMA	<u>Group D</u> LAMA or LAMA+LABA or ICS+LABA
0-1 outpatient exacerbations (steroid ± antibiotic)	<u>Group A</u> Bronchodilator	<u>Group B</u> LAMA or LABA
	mMRC 0-1 or CAT<10	mMRC ≥2 or CAT≥10

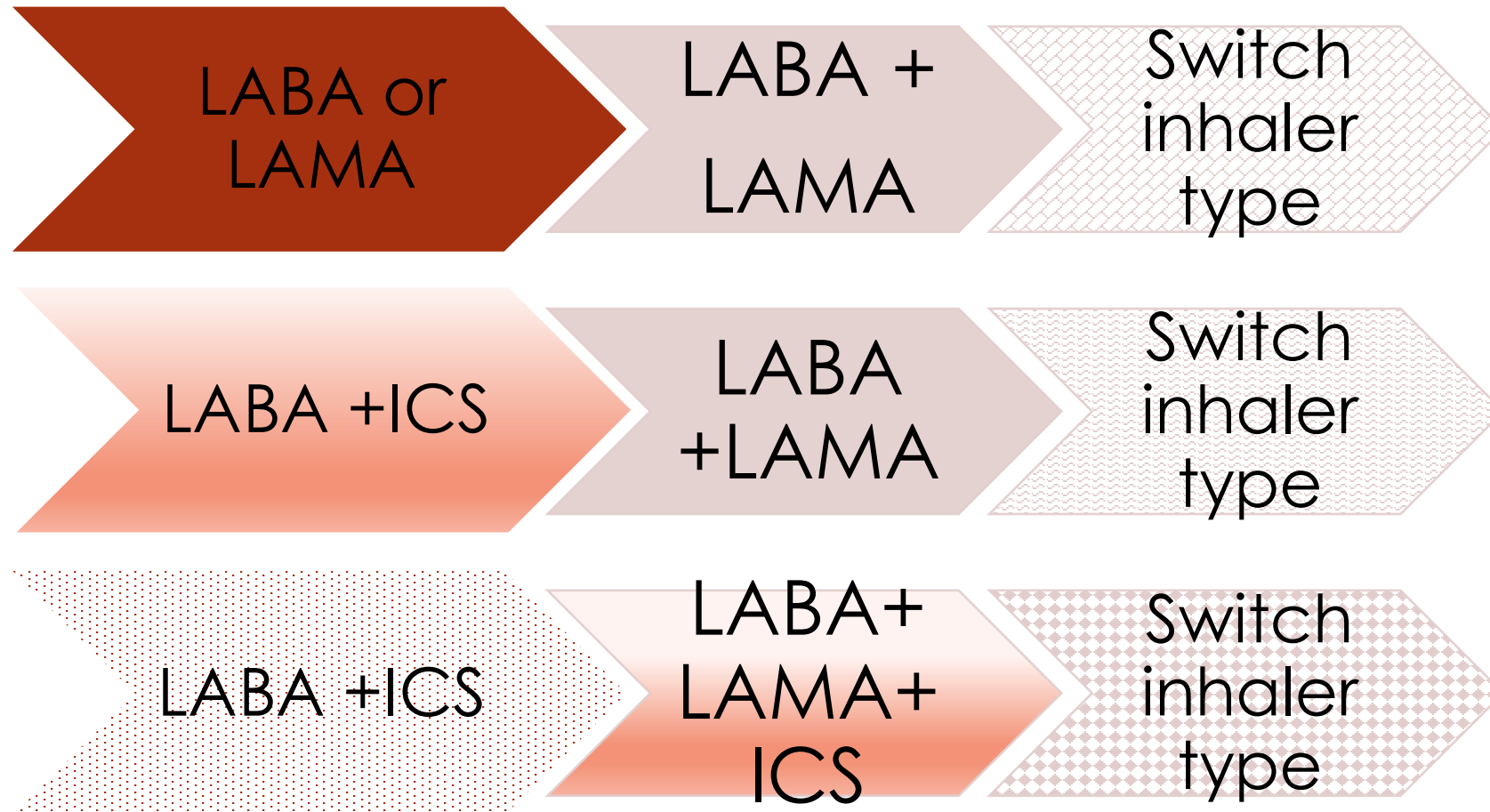
GOLD Follow-Up Treatment for Exacerbations **Without Eosinophils**



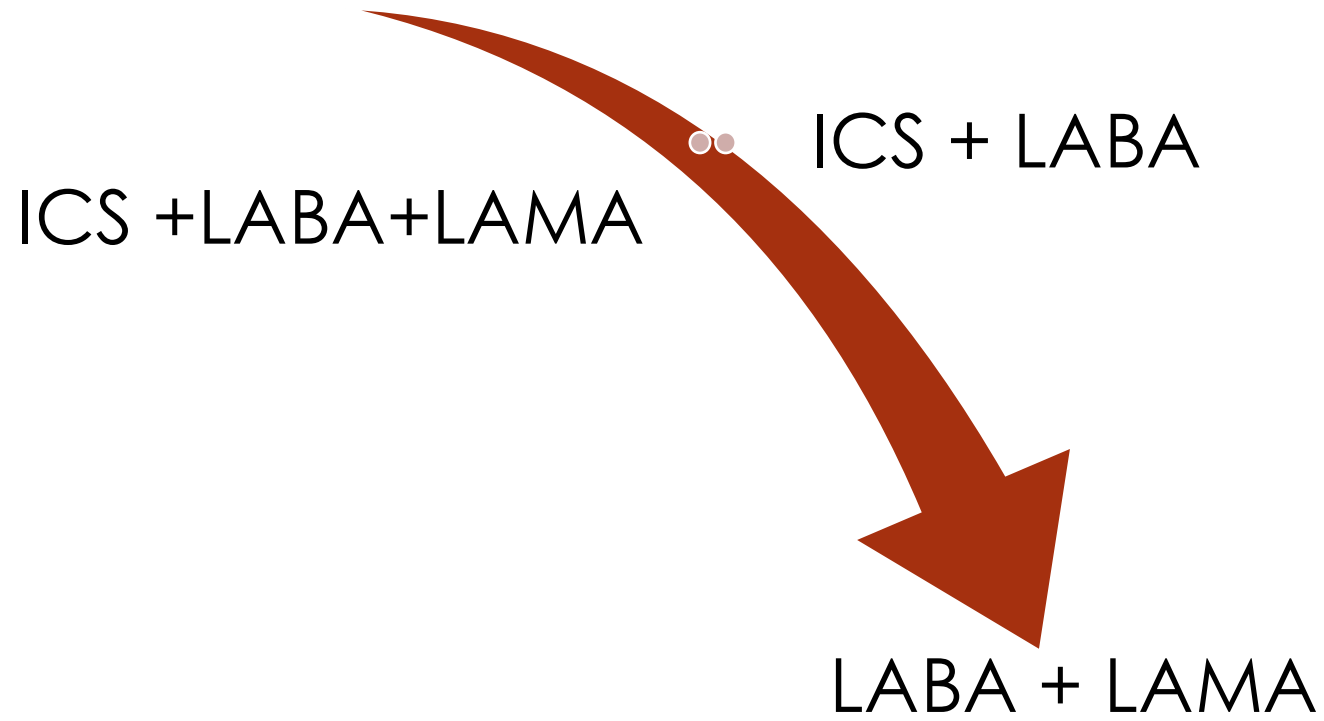
GOLD Follow-Up Treatment for Exacerbations **With Eosinophils**



GOLD Follow-Up Treatment for DYS-PNEA



GOLD Follow Up De-escalation



Exacerbation

Asthma

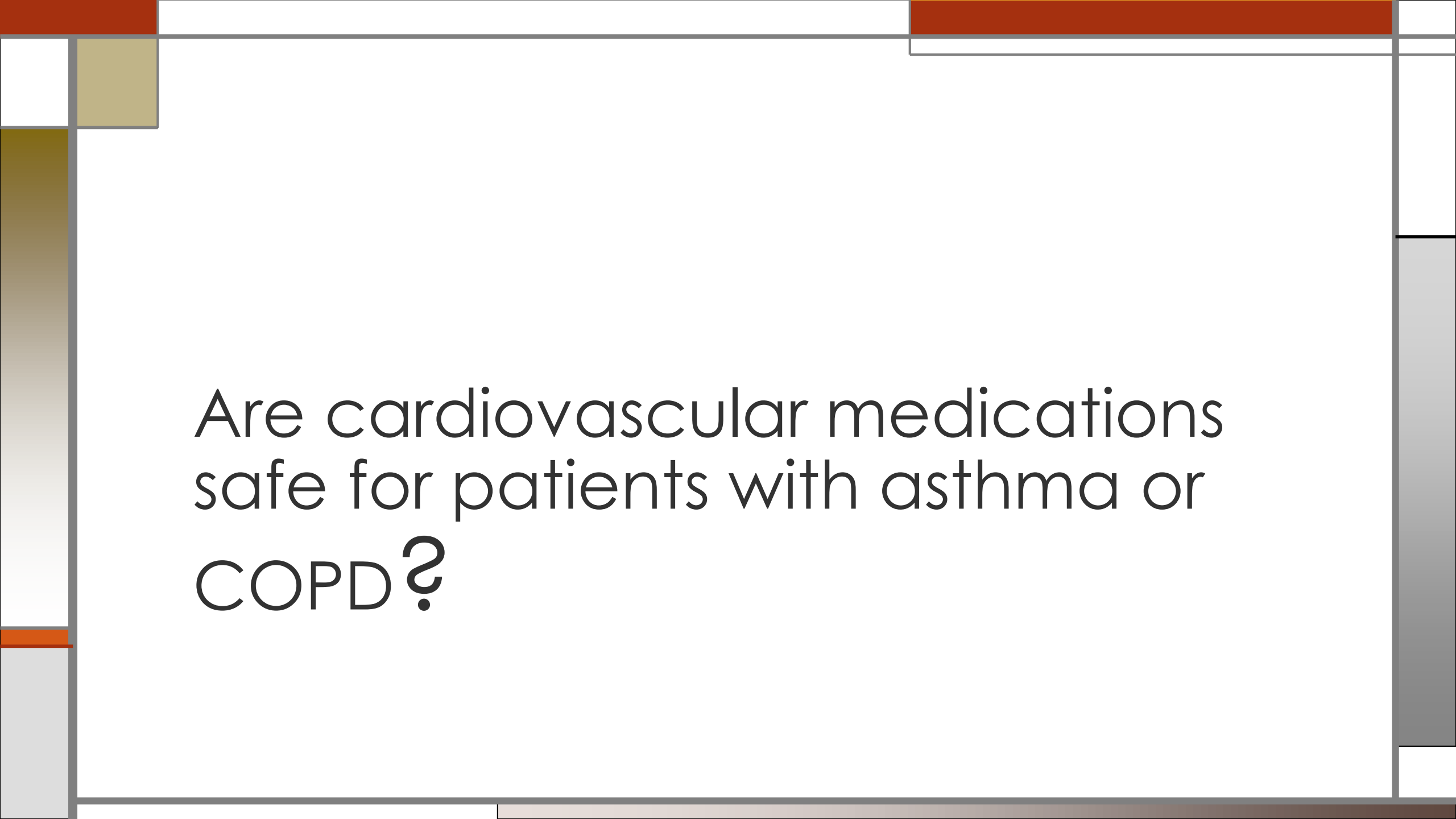
- Oxygen if needed
- SABA
 - MDI or nebulization
- Corticosteroid
 - PO preferred or IV/IM
 - Short course, low dose
- +/- Ipratropium
- ICS

COPD

- Oxygen if needed
- SABA
 - MDI or nebulization
- Corticosteroid
 - PO preferred or IV/IM
 - Short course, low dose
- +/- Antibiotic

Health Maintenance

- Smoking Cessation
- Immunizations
- Pulmonary Rehabilitation



Are cardiovascular medications
safe for patients with asthma or
COPD?

Clinical Case Question

- Ms. K has a STEMI. Which of the following is likely to make Ms. K's asthma and COPD worse?
 - A. Metoprolol 25 mg PO daily
 - B. Atorvastatin 80 mg PO daily
 - C. Aspirin 81 mg PO daily

Neuronal Innervations of the Lungs

- Parasympathetic
 - Releases acetylcholine
 - Ach binds to muscarinic receptors
 - Bronchoconstriction
- Sympathetic
 - No direct innervation to airway smooth muscle

β -Blockers for Asthma and COPD

Selective for β_1

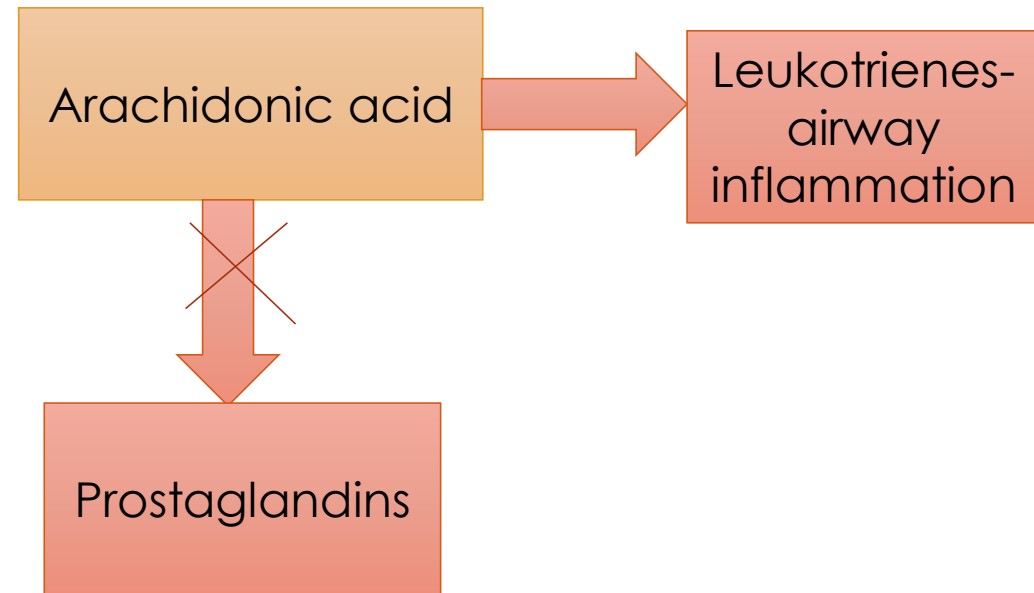
- Metoprolol
- Atenolol
- Acebutolol
- Betaxolol
- Bisoprolol
- Esmolol
- Nebivolol

Non-selective for β_1

- Carvedilol
- Propranolol
- Labetolol
- Carteolol
- Nadolol
- Timolol
- Sotalol
- Pindolol
- Penbutolol

Potential Drug Interactions

- NSAIDS (ketorolac, naproxen, aspirin, ibuprofen)
- Bronchoconstriction
 - Asthma
 - Sinusitis
 - Nasal polys



Montelukast

- Use
- MOA
 - Blocks cysteinyl leukotrienes (LT), inflammation
 - Animal studies: inhibit atherosclerosis, intimal hyperplasia, vascular injury
 - Genetic variants of LT pathway, increased risk of MI and stroke
- Cardiovascular outcomes
 - Decreased risk of recurrent stroke in patients not taking ACE or ARB
 - HR (95% CI) 0.34 (0.14-0.82)
 - Lower risk of recurrent MI in male patients (*post hoc* analysis)
 - HR (95% CI) 0.65 (0.43-0.99) P value .046

Clinical Case Question

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Clinical Case Question

- Ms. K would like to quit smoking.
 - Which of the following is the most effective treatment for tobacco dependence?
- A. Nicotine patch
 - B. Bupropion
 - C. Varenicline

Lung Health Study

- 5 year prospective trial
- Treatment arms
 - Smoking cessation + ipratropium tid
 - Smoking cessation alone
 - No intervention
- 11 year follow-up
- Results
 - 18% reduction in all cause mortality
 - Smoking-cessation is the only long-term intervention to affect long-term decline in FEV1
 - Only intervention to slow the progression of COPD

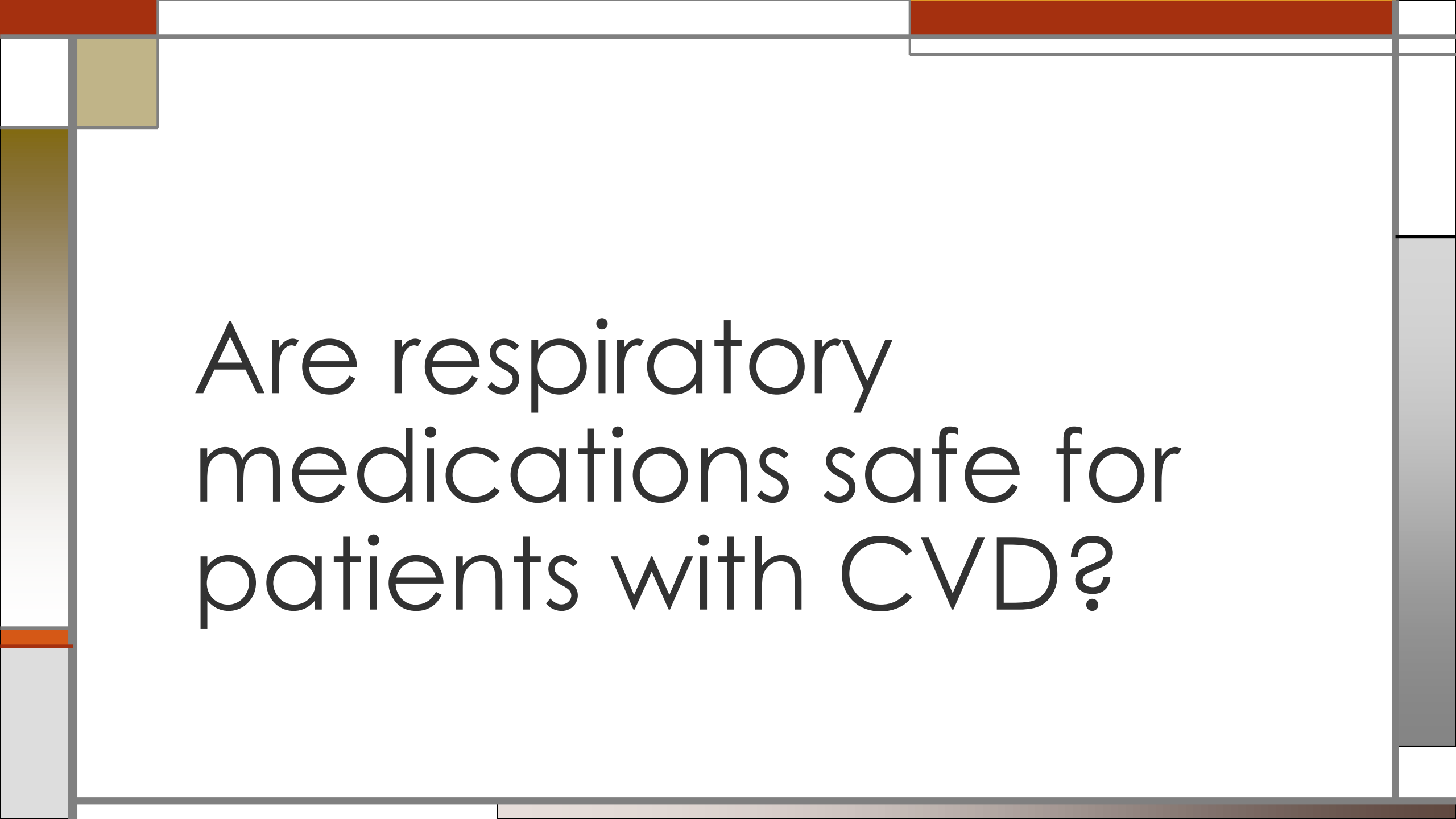
Tobacco dependence in CVD

	NRT	Bupropion	Varenicline
Safe	Limited acute event data (>2 wks) SAE 5.4% placebo 7.9% MACE 11.9% placebo 9.7% Safety similar to bupropion, varenicline and placebo in chronic CVD	Limited acute event data SAE 17.7% placebo 18.5% MACE 13% placebo 11% Safety similar to NRT, varenicline and placebo in chronic CVD	Evidence lacking for acute event SAE 11.9% placebo 11.3% MACE 4% placebo 4.6% Safety similar to NRT, bupropion and placebo in chronic CVD
Effective	No	No Similar to "cold turkey" post MI	Yes NNT=10

Eisenberg MJ. Circulation 2016;133:21-30. Benowitz NL. JAMA Intern Med. doi:10.1001/jamainternmed.2018.0397. Eisenberg MJ. J Am Coll Cardiol 2013;61;524-32. Joseph AM. N Engl J Med 1996; 335:1792-8.

Clinical Case Question

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Are respiratory
medications safe for
patients with CVD?

Clinical Case Question

- Ms. K is complaining about heart palpitations with the use of her OTC asthma medication.
 - Which of the following beta agonists is not selective at the β_2 -receptor in the lungs?
- A. Albuterol
 - B. Levalbuterol
 - C. Epinephrine

Short-acting (SABA) and Long-acting β_2 -agonist (LABA)

- Examples
 - Albuterol, levalbuterol (SABA), epinephrine
 - Arformoterol, formoterol, indacaterol, salmeterol, olodaterol, vilanterol (LABA)
- Cardiovascular concerns:
 - Induction of arrhythmias
 - Reflex activation of adrenergic mechanism
 - Worsening heart failure associated with left ventricular systolic dysfunction
 - Hypokalemia
 - Hypoxemia

SABA use and CVD Outcomes in Patients with Asthma

	Age-adjusted Event Rate	Hazard Ratio (95%CI)	P value
All coronary heart disease (N=50,634)	77	0.33 (0.30-0.37)	<0.0001
All cerebrovascular disease (N=52,614)	36	0.37 (0.33-0.43)	<0.0001
Heart failure (N=52,749)	65	0.62 (0.56-0.68)	<0.0001
All cause mortality (N=53,175)	234	2.24 (2.13-2.37)	<0.0001

Epinephrine Inhalation Solution

- OTC
- Non-selective β_1 and β_2
- Not recommended in asthma or COPD guidelines
- Published trials lacking

Clinical Case Question

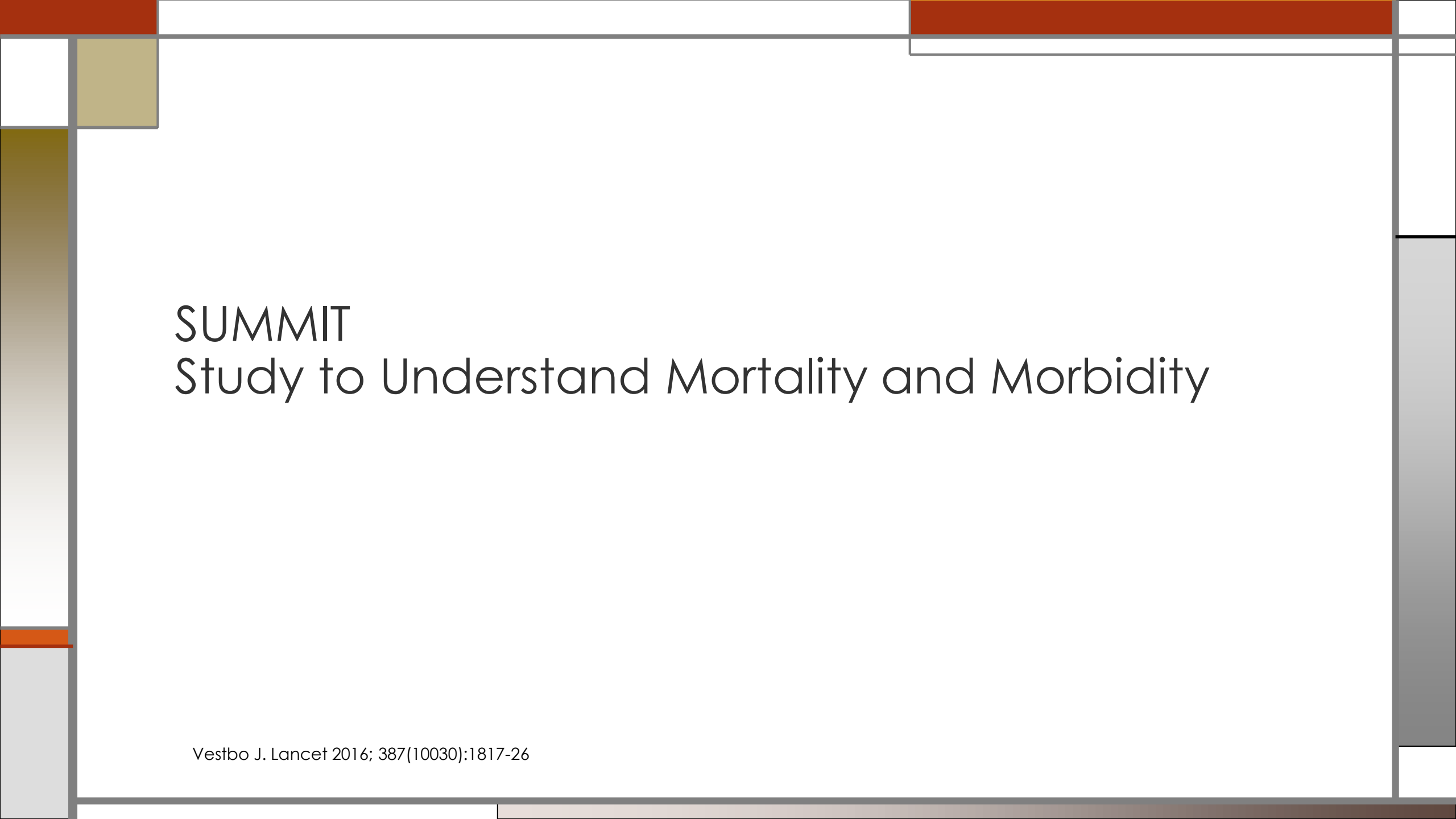
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Clinical Case

- Ms. K is non-adherent to her respiratory medications.
 - Which of the following treatments for **COPD** decreases mortality?
- A. ICS
 - B. LABA
 - C. ICS/LABA
 - D. None of the above

Inhaled Corticosteroids (ICS) and Long-acting β 2-agonists (LABA)

- Examples
 - Fluticasone propionate/salmeterol, fluticasone furoate/vilanterol, mometasone/formoterol, budesonide/formoterol,
 - Cardiovascular concerns
 - Hypokalemia (both ICS and LABA)
- LABA component
- Sinus tachycardia
 - Coronary ischemia
 - QT prolongation
 - Palpitation
 - Hypertension



SUMMIT

Study to Understand Mortality and Morbidity

Vestbo J. Lancet 2016; 387(10030):1817-26

Methods SUMMIT

- Purpose:
 - ICS/LABA improve survival in patients with moderate COPD and cardiovascular risk
- Prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter
- Four treatment groups
 - Placebo
 - Fluticasone furoate 100 mcg
 - Vilanterol 25 mcg
 - Fluticasone furoate 100 mcg/vilanterol 25 mcg
- Primary end-point: All-cause mortality
- 1.8 years (2011-2015)

Study Subject Characteristics SUMMIT

- 16,485 ITT (16,568 total)
- 65 years old
- 25% women
- 81% white
- BMI 28 kg/m²
- 47% current smokers
- GOLD stage 2 COPD
- 66% had CVD
- 34% high risk CVD

Results SUMMIT

	Placebo	Fluticasone	Vilanterol	Combo	p-value Fluticasone/ Vilanterol vs. placebo
Mortality	275 (6.7%)	251 (6.1%)	265 (6.4%)	246 (6%)	0.137
Cardiovascular endpoints (MI, stroke, TIA, angina, death)	173 (4.2%)	161 (3.9%)	180 (4.4%)	174 (4.2%)	0.478

Conclusion SUMMIT

- Fluticasone furoate and vilanterol did not affect mortality or cardiovascular outcomes in patients with moderate COPD and heightened cardiovascular risk

SUMMIT Post-hoc DESCRIPTIVE analysis

- No excess CV risk with ICS, LABA or ICS/LABA
- No evidence β -blocker therapy reducing respiratory benefit
- COPD hospitalizations increase the risk for CVD events
- ICS/LABA reduced rates of corticosteroids, corticosteroids + antibiotics but not antibiotics alone
- ICS/LABA use prior to study and randomized to treatment instead of placebo affected mortality but not exacerbations
- ICS alone or with LABA slowed FEV1 decline
- ICS/LABA had no impact on mortality but showed a trend to decrease exacerbations

Brook RD. Heart 2017;103(19):1536-42. Dransfield MT. Ann AmThorac Soc 2018;15(5):608-614. Martinez FJ. Am J Respir Crit Care Med 2017;195(7):881-888. Vestbo J. ERJ Open Res 2019;5(1):00203. Celli B. AJRCCM 2018;197(12).

Clinical Case

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 - C. ICS/LABA
 - D. None of the above

Short-acting (SAMA) and Long-acting (LAMA) muscarinic antagonist

- Examples
 - Ipratropium (SAMA) non-selective
 - Tiotropium, Acclidinium, Glycopyrrolate, Revefenacin, Umeclidinium (LAMA)
- Cardiovascular concerns
 - Sinus tachycardia
 - Arrhythmia

Ipratropium

- Lung Health Study
 - CVD death and supraventricular tachycardia with ipratropium and COPD
- 82,717 US veterans
 - Any exposure to anticholinergic within past 6 months was associated with increased risk of CVE HR (95%CI 1.40 (1.13-1.51)
 - 44% heart failure, 28% acute coronary syndrome, 28% dysrhythmia
 - >6 months no association with CVE and anticholinergics

UPLIFT Trial- Tiotropium

AE	Tiotropium (N=2986)	Placebo (N=3006)	RR Tio vs. Placebo (95%CI)
A. fib	0.74	0.77	0.95 (0.68-1.33)
CHF	0.29	0.48	0.59* (0.37-0.96)
MI	0.69	0.97	0.71* (0.52-0.99)

Tashkin DP. N Engl J Med 2008;359:1543-54

UPLIFT Conclusions

- Tiotropium does not slow down the rate of decline in FEV₁
- Tiotropium does decrease the number of COPD exacerbations
- Tiotropium use is associated with a reduction in cardiac adverse events
 - 50% were on anticholinergic prior to enrollment

TIOSPIR Trial- Tiotropium

	Tio Respimat 2.5 mcg	Tio Respimat 5 mcg	Tio Handihaler (control) 18 mcg
Previous cardiac arrhythmia	79 (13.1%) (N=604)	65 (10.6%) (N=614)	78 (12.9%) (N=607)
Death from cardiovascular causes	2.1%	2%	1.8%
MACE	3.9%	3.9%	3.6%

Long-acting muscarinic antagonist (LAMA) and Long-acting β 2-agonist (LABA)

- Examples
 - Tiotropium/olodaterol, Glycopyrrolate/formoterol, Glycopyrrolate/indacaterol, Umeclidinium/vilanterol
- Cardiovascular concerns
 - Sinus tachycardia
 - Coronary ischemia
 - QT prolongation
 - Palpitation
 - Hypokalemia
 - Hypertension

LABA and LAMA Induced Cardiovascular Event in COPD

- CAD, arrhythmia and heart failure
 - Nested case control
 - 284,220 subjects
 - 2007-2011
 - LAMA or LABA naïve patients
 - 1.5 fold increase in severe cardiovascular risk (95% CI, 1.35-1.67; $p < 0.001$)
 - CAD and HF, arrhythmia (LAMA not LABA), not significant for stroke
 - Previous LABA and LAMA use
 - 9-12% reduction CVE

Bronchodilator	Number needed to harm (95%CI)
LABA new	406 (303-508)
LAMA new	391 (254-725)
LABA & LAMA new	198 (107-483)

Clinical Case

- Ms. K has another asthma and COPD exacerbation
 - Which step-up therapy is effective and safest for cardiovascular outcomes?
- A. Oral corticosteroids
 - B. Azithromycin
 - C. Roflumilast
 - D. Theophylline

Oral Corticosteroid use and CVD Outcomes in Patients with Asthma

	Age-adjusted Event Rate	Hazard Ratio (95%CI)	P value
All coronary heart disease (N=35,768)	896	2.59 (2.49-2.69)	<0.0001
All cerebrovascular disease (N=40,445)	286	1.91 (1.81-2.01)	<0.0001
Heart failure (N=40,245)	571	3.48 (3.34-3.63)	<0.0001
All cause mortality (N=41,555)	468	2.64 (2.55-2.75)	<0.0001

Oral Corticosteroid and CVD

- Use
- MI risk
 - 5 days after Rx for antibiotic AND steroid
- Stroke risk
 - 49 days after antibiotic OR steroid
- Cardiovascular effects:
 - HTN
 - Cardiac arrest
 - Cardiac rupture after MI
 - CHF
 - Shock
 - Syncope

Roflumilast

- Use
 - PDE4, anti-inflammatory
 - Add-on treatment to reduce COPD exacerbations
- Cardiovascular outcomes
 - TNF, IL-6, C-reactive protein
 - May reduce vascular inflammation?
 - Relative reduction in cardiovascular death, non-fatal MI, and non-fatal stroke compared with placebo was 35%
 - Prospective, double-blind, post-marketing study underway

Azithromycin

- Use
 - Decreases COPD and asthma exacerbations
 - Dosed daily or 3x weekly for one year
 - Effective in non-smokers
- Cardiovascular side effects:
 - Prolonged cardiac repolarization
 - QT prolongation
 - Cardiac dysrhythmias
 - Torsades de pointes
- Excluded from studies ECG abnormalities, QTc>0.48s, meds prolong QT

Theophylline

- Use
 - Rarely used in clinical practice
 - Caffeine-like structure
 - Improves
 - Pulmonary vascular resistance
 - Pulmonary arterial pressure
 - Very narrow therapeutic range (8-12 mcg/mL)
 - Lower dose needed in heart failure patient among others
- Cardiovascular effects:
 - Increases
 - heart rate
 - atrial automaticity
 - Intracardiac conduction
 - Serum concentrations >30 mcg/mL
 - Sinus tachycardia
 - Ventricular premature beats
 - Ventricular tachycardia

Clinical Case

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- A. Oral corticosteroids
 - B. Azithromycin
 - C. Roflumilast
 - D. Theophylline

Summary

- Follow guidelines for heart failure, ischemic heart disease, hypertension for COPD patients
- Use selective beta-blockers and screen for ASA sensitivity in patients with asthma
- Promote tobacco cessation and treat tobacco dependence
- Use caution with newly prescribed respiratory medications and increased risk of cardiovascular events

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Questions?

Post-Test Questions

1. Which of the following beta-blockers is safe to use in a patient with asthma?
 - A. Propranolol
 - B. Labetalol
 - C. Metoprolol
 - D. Carvedilol

2. Which of the following respiratory medications may prolong the QT interval?
 - A. Azithromycin
 - B. Montelukast
 - C. Tiotropium
 - D. Fluticasone

3. Which medication for tobacco dependence is effective in patients with CVD?
 - A. Nicotine patch
 - B. Bupropion
 - C. Varenicline
 - D. Nicotine gum

4. Which beta-agonist is most likely to increase heart rate?
 - A. Albuterol
 - B. Epinephrine
 - C. Levalbuterol
 - D. Formoterol