Clinical Guideline Update: What's new with Diabetes, Dyslipidemia, and COPD Management?

PLU Pharmacotherapeutic Update for Providers
May 6, 2023

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Disclosure

T. Levi Lancaster, PharmD has no actual or potential conflict of interest in relation to this program/presentation.

I will not discuss off label use and/or investigational use in our presentation.

Objectives

At the completion of this program, the pharmacist and pharmacy technicians will be able to:

- Identify practice guidelines that have changed in the last year
- Discuss relevant updates and changes to practice guidelines
- Discuss modifications to their practices based on changes to guidelines

Presentation Roadmap

When poll is active, respond at **PollEv.com/levil606**

Text **LEVIL606** to **37607** once to join

Diabetes Updates

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Summary of Changes – 2023 ADA Standards of Care

- Emphasis on supporting higher weight loss (up to 15%) based on the efficacy of and access to newer medications when appropriate
- New recommendations related to **sleep health and physical activity** in people with diabetes
- Broad consideration of **social determinants of health** in guiding the design and delivery of care
- New **hypertension diagnosis cut-offs** (hypertension is now defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥80 mmHg)
- The **expanded role of SGLT2 inhibitor use** in preserved and reduced heart failure ejection fraction
- The **role of finerenone** in individuals with diabetes and chronic kidney disease with albuminuria
- New **lipid management recommendations** suggesting lower LDL goals for high-risk individuals

Diabetes Care 2022;46(Supplement 1):S1-S280.

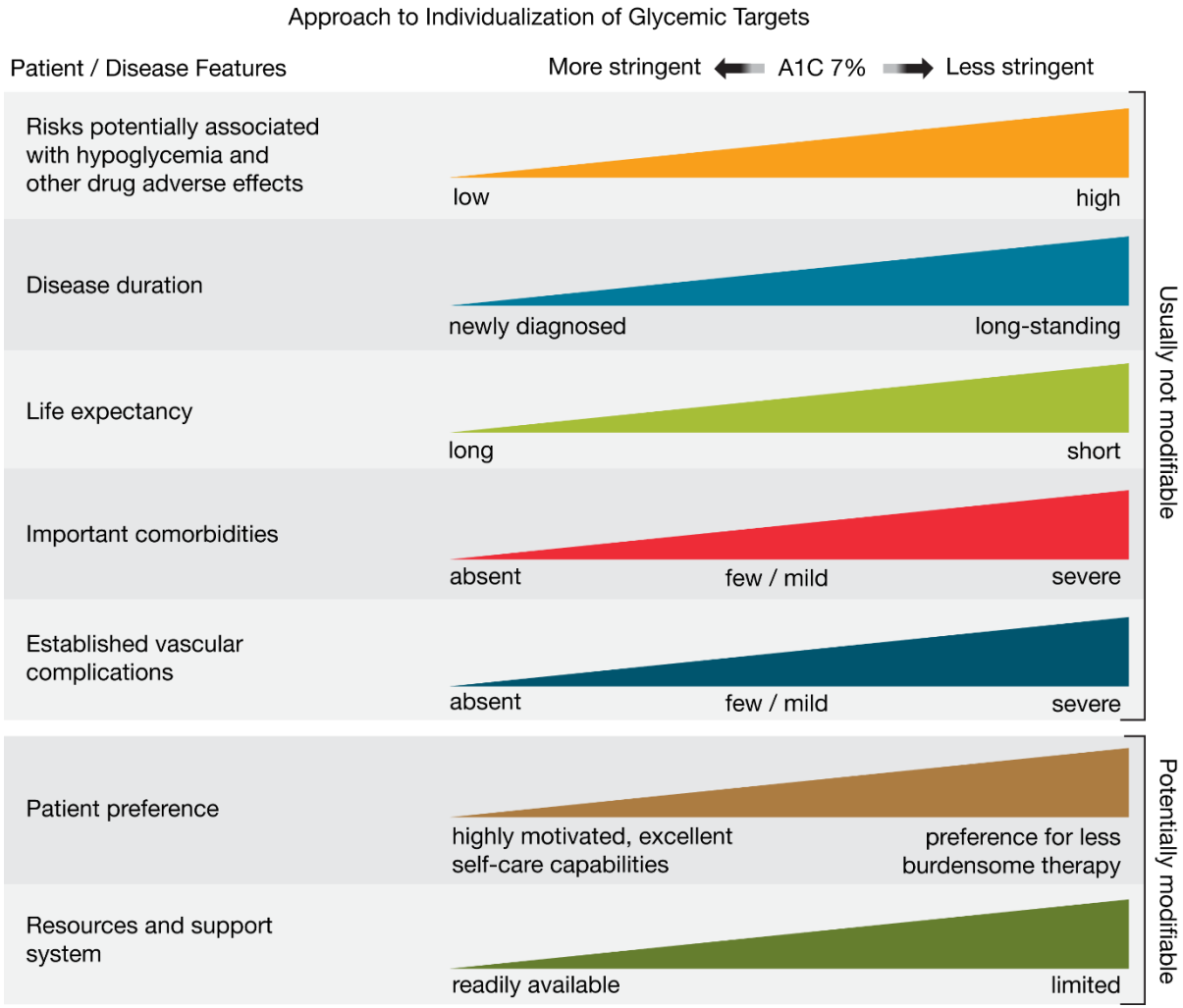
Glycemic Targets

ADA Recommendation 6.5 (Updated)

For those with frailty or at high risk of hypoglycemia, a target of >50% time in range with < 1% time below range is recommended. (LOE B)

ADA Recommendation 6.9 (NEW)

Setting a glycemic goal during consultations is likely to improve patient outcomes. (LOE E)



Diabetes Care 2022;46(Supplement 1):S1-S280.

CGM Eligibility

Medicare Requirements:

- On any insulin
- Multiple level 2 hypoglycemic events
- One single level 3 hypoglycemic event

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit — EITHER/OR — SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If A1C above target

Diabetes Care 2022;46(Supplement 1):S1-S280.

Pioglitazone CV Benefits

ADA Recommendation 3.10 (New)

"In people with a history of stroke and evidence of insulin resistance and prediabetes, pioglitazone may be considered to lower the risk of stroke or myocardial infarction. However, this benefit needs to be balanced with the increased risk of weight gain, edema, and fracture. (LOE A) Lower doses may mitigate the risk of adverse effects. (LOE C)"

Diabetes Care 2022;46(Supplement 1):S1-S280.

Pioglitazone CV Benefits

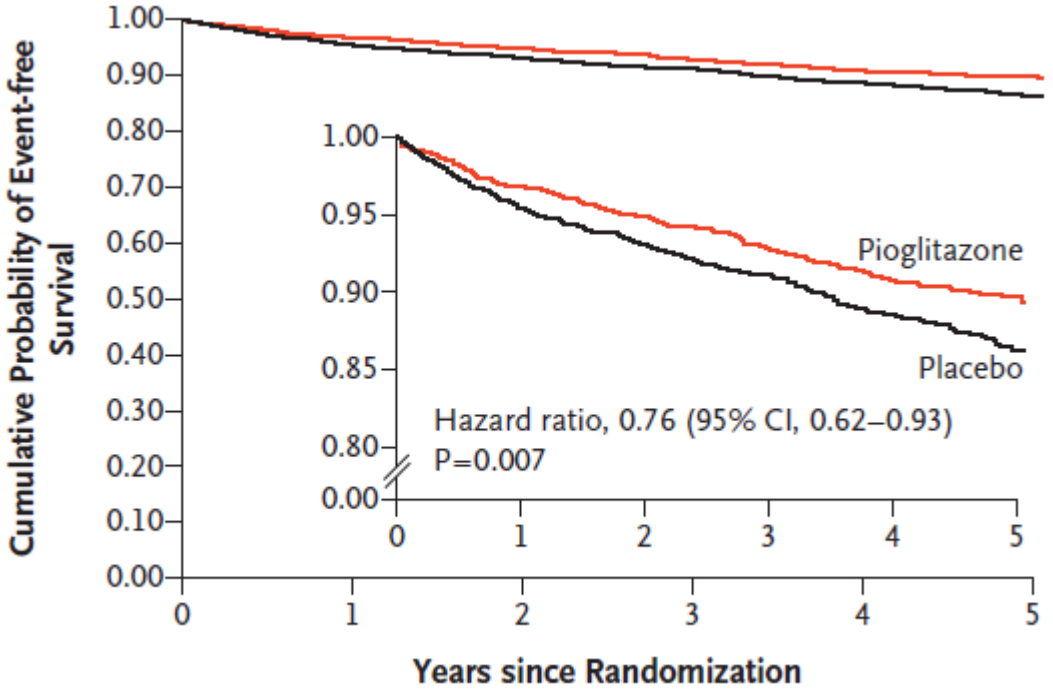
ORIGINAL ARTICLE

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

W.N. Kernan, C.M. Viscoli, K.L. Furie, L.H. Young, S.E. Inzucchi, M. Gorman, P.D. Guarino, A.M. Lovejoy, P.N. Peduzzi, R. Conwit, L.M. Brass,* G.G. Schwartz, H.P. Adams, Jr., L. Berger, A. Carolei, W. Clark, B. Coull, G.A. Ford, D. Kleindorfer, J.R. O'Leary, M.W. Parsons, P. Ringleb, S. Sen, J.D. Spence, D. Tanne, D. Wang, and T.R. Winder, for the IRIS Trial Investigators†

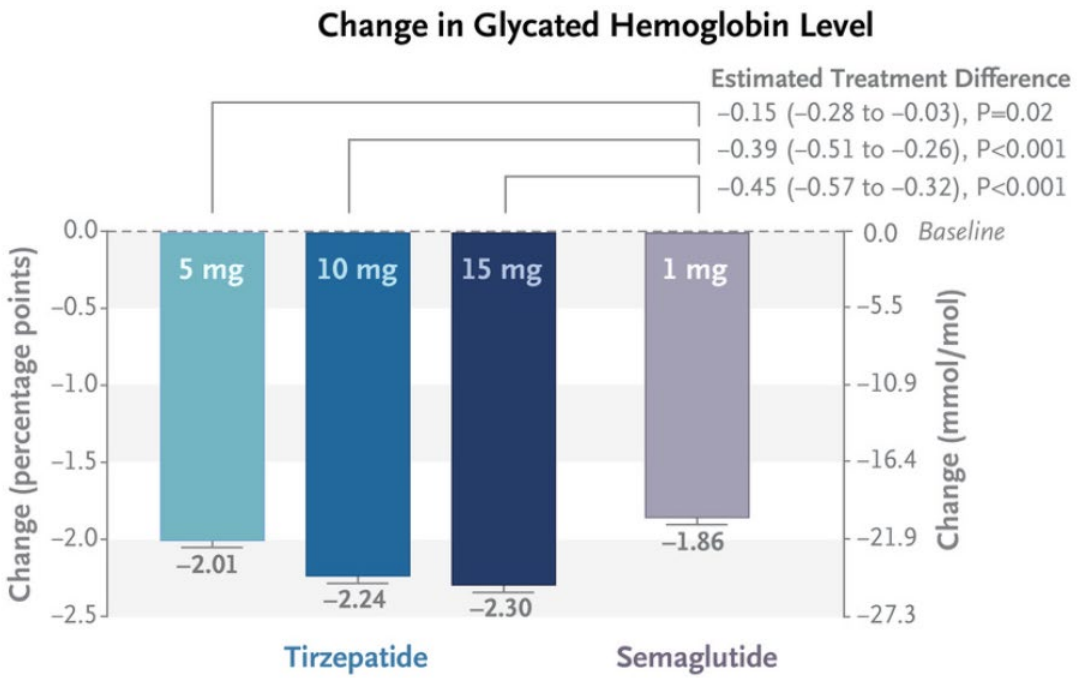
IRIS Trial

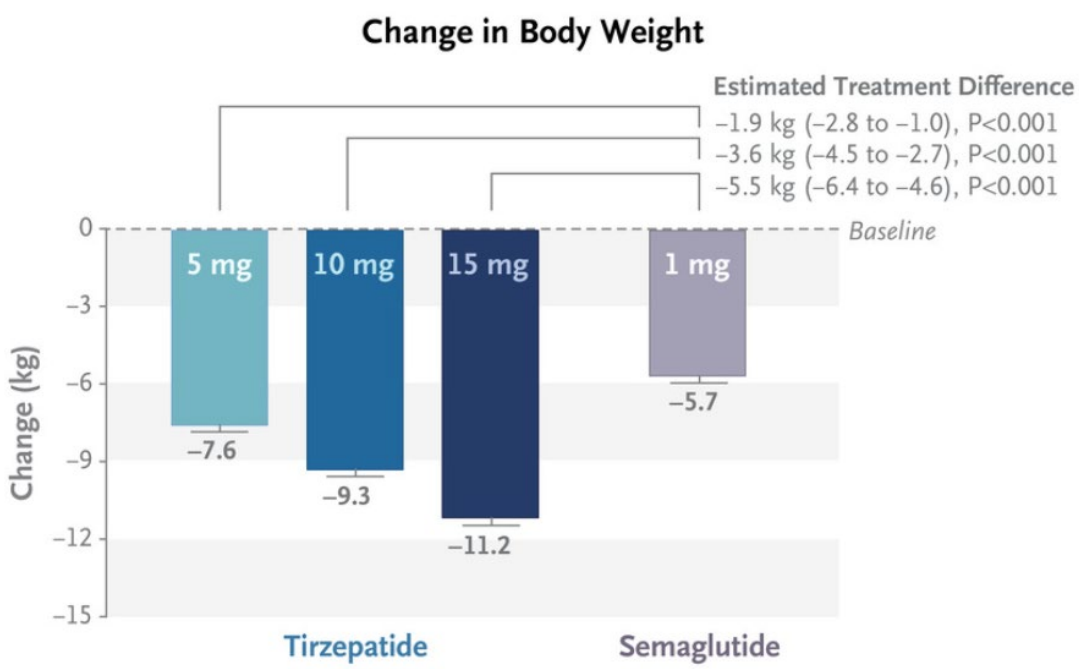
- 3876 patients randomized to either:
  - Pioglitazone 45 mg daily
  - Placebo daily
- Patients were 40 years or older with a CVA or TIA in the last 6 months
- Primary Outcome: first fatal or non-fatal stroke or myocardial infarction



NEJM 2016; 374:1321-31.

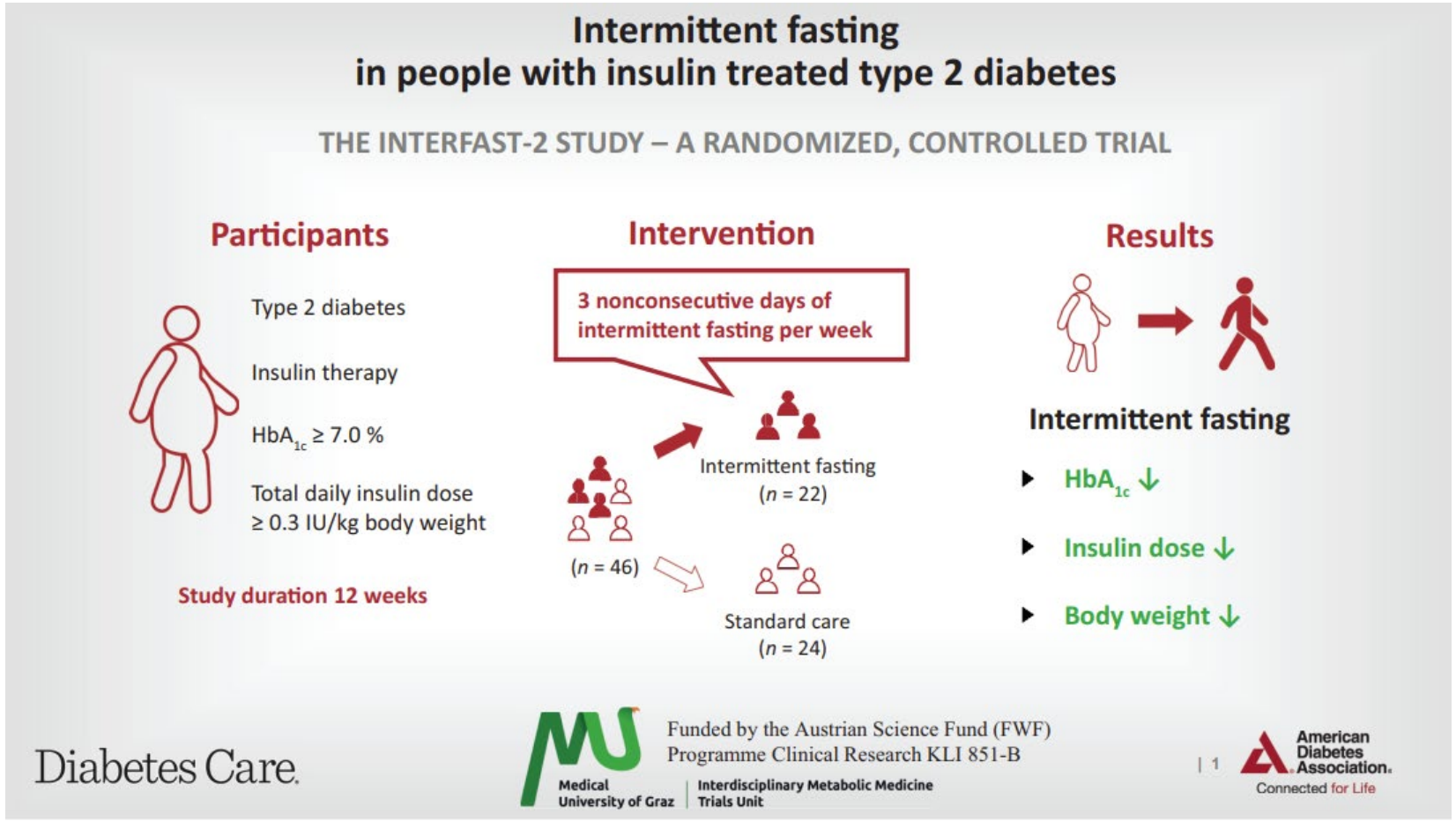
New Kid on the Block: Tirzepatide





N Engl J Med 2021 Aug 5;385(6):503-515.

Intermittent Fasting



Diabetes Care 2023;46(2):463–468.

CGM Interfering Substances

Table 7.4—Continuous glucose monitoring devices interfering substances

Medication	Systems affected	Effect
Acetaminophen		
>4 g/day	Dexcom G6	Higher sensor readings than actual glucose
Any dose	Medtronic Guardian	Higher sensor readings than actual glucose
Alcohol	Medtronic Guardian	Sensor readings may be higher than actual glucose
Ascorbic acid (vitamin C), >500 mg/day	FreeStyle Libre	Higher sensor readings than actual glucose
Hydroxyurea	Dexcom G6, Medtronic Guardian	Higher sensor readings than actual glucose
Mannitol	Senseonics Eversense	Sensor bias within therapeutic concentration ranges
Tetracycline	Senseonics Eversense	Sensor bias within therapeutic concentration ranges

Diabetes Care 2022;46(Supplement 1):S1-S280.

Cholesterol Management

ADA Recommendation 10.20 (Updated)

For those age 40-75 with diabetes and high risk for CV events (1 or more CV risk factor), use high intensity statin to target LDL < 70 mg/dL

ADA Recommendation 10.26 (Updated)

For those with established CV disease and diabetes, use high intensity statin or other lipid-lowering agents to target LDL < 55 mg/dL

Diabetes Care 2022;46(Supplement 1):S1-S280.

Blood Pressure Management

ADA Recommendation 10.4 (Updated)

People with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥ 130/80 mmHg. The on-treatment target blood pressure goal is < 130/80 mmHg, if it can be safely attained.

STEP (34)	8,511 participants aged 60–80 years, including 1,627 with diabetes	SBP target: <130 mmHg Achieved (mean): 127.5 mmHg	SBP target: <150 mmHg Achieved (mean): 135.3 mmHg	• Intensive SBP target lowered risk of the primary composite outcome 26% (stroke, ACS [acute MI and hospitalization for unstable angina], acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes) • Intensive target reduced risk of cardiovascular death 28% • Intensive therapy increased risks of hypotension

Diabetes Care 2022;46(Supplement 1):S1-S280.

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Patient Case #1

TJ is a 62 yo male with type 2 diabetes, heart failure, coronary artery disease with history of stent placement 2 years prior, and hypertension. Labs have been WNL. A1C was 6.7% two weeks ago. Diabetes is currently managed with Metformin XR 2000 mg daily with food and Insulin Glargine 64 units nightly. He is also taking Losartan 100 mg nightly, Rosuvastatin 10 mg nightly, Metoprolol Succinate 100 mg daily, and Aspirin 81 mg daily. He has occasional hypoglycemia about once weekly in the morning or prior to lunch. Vitals are stable and within goal range today.

What changes would you make to his current diabetes regimen?

A. Start Liraglutide 1.8 mg daily before breakfast and decrease insulin

B. Start Pioglitazone 15 mg daily

C. Start Empagliflozin 10 mg every morning

D. No changes; diabetes is well controlled with A1C of 6.4%

Summary – Diabetes Update

Medication selection for diabetes should continue to prioritize therapies with proven benefit in select comorbidities (Cardiovascular Disease, Heart Failure, Chronic Kidney Disease, Obesity)

Pioglitazone should be considered as an anti-diabetes agent to reduce CV risk in high-risk patients

Intermittent fasting diets may be considered for select, low-risk patients with insulin-treated diabetes

Cholesterol should be managed with a goal of less than 70 mg/dL or less than 55 mg/dL for those at high risk of CV disease or with existing CV disease, respectively

Blood pressure should be managed to target a goal of < 130/80 mmHg

Dyslipidemia Updates

Role of Nonstatin Therapies for LDL-Cholesterol Lowering

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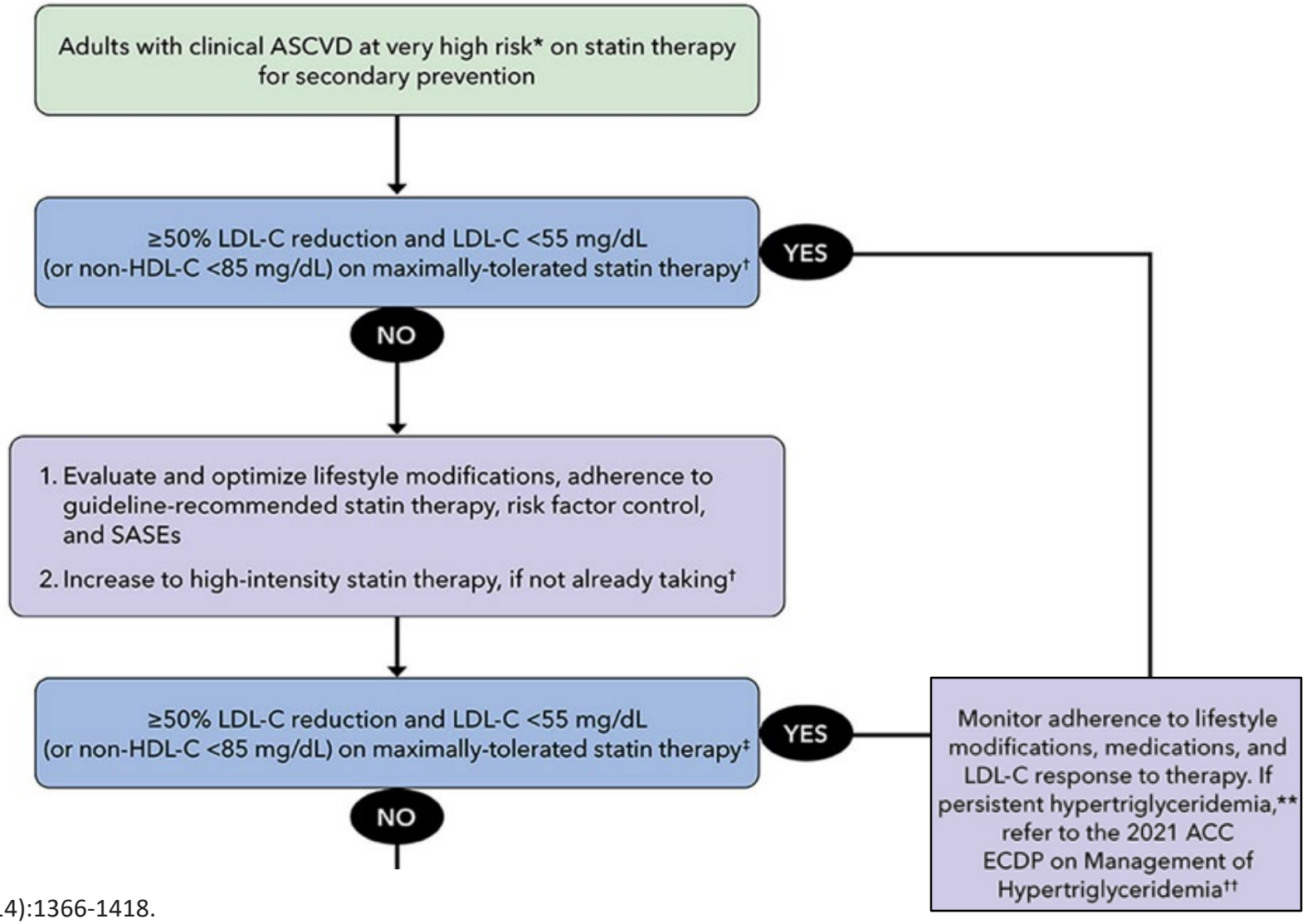
AHA/ACC Cholesterol Guidelines

Four groups should receive statin therapy:

1. Clinical ASCVD
   High-intensity statin
2. Primary prevention – primary LDL-C ≥190 mg/dL
   High-intensity statin
3. Primary prevention – diabetes 40-75 years of age and LDL-C 70-189 mg/dL
   Moderate-intensity statin if 10-year ASCVD risk < 7.5%
   High-intensity statin if 10-year ASCVD risk ≥ 7.5%
4. Primary prevention – no diabetes 40-75 years of age and LDL-C 70-189 mg/dL
   Moderate to High-intensity statin

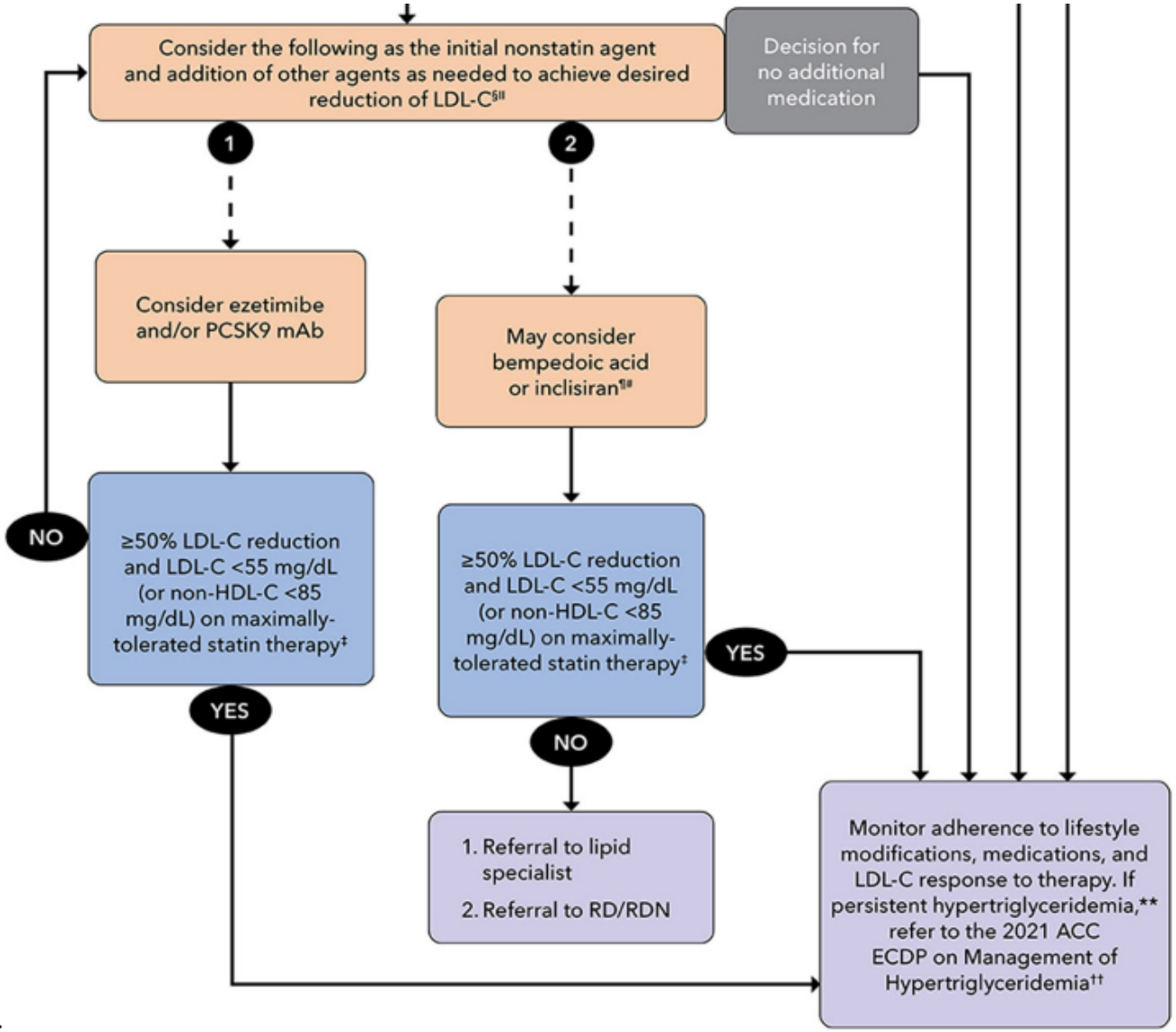
Circulation 2019 Jun 18;139(25):e1082-e1143.
J Am Coll Cardiol 2022 Oct 4;80(14):1366-1418.

2022 Algorithm for Very High CV Risk



J Am Coll Cardiol 2022 Oct 4;80(14):1366-1418.

2022 Algorithm for Very High CV Risk



J Am Coll Cardiol 2022 Oct 4;80(14):1366-1418.

Cardiovascular Risk Factors

TABLE 1 Criteria for Defining Patients at Very High Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 months)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic PAD (history of claudication with ABI <0.85 or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. Reprinted with permission from Grundy et al.[7]

ABI = ankle-brachial index; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease

Risk-Enhancing Factors

- **Family history of premature ASCVD** (men aged <55 years; women aged <65 years)
- **Primary hypercholesterolemia** (LDL-C 160-189 mg/dL [4.1-4.8 mmol/L); non-HDL-C 190-219 mg/dL [4.9-5.6 mmol/L]*
- **Metabolic syndrome** (increased waist circumference, elevated triglycerides [≥150 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women] are factors; tally of 3 makes the diagnosis
- **Chronic kidney disease** (eGFR 15-59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
- **History of premature menopause (before age 40 years) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia**
- **High-risk races/ethnicities** (eg, South-Asian ancestry)
- **Lipids/biomarkers:** Associated with increased ASCVD risk
  - **Persistently* elevated, primary hypertriglyceridemia** (≥175 mg/dL)
  - If measured:
    1. **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
    2. **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).
    3. **Elevated apoB ≥130 mg/dL:** A relative indication for its measurement would be triglycerides ≥200 mg/dL. A level ≥130 mg/dL corresponds to LDL-C ≥160 mg/dL and constitutes a risk-enhancing factor
    4. **ABI** <0.9

J Am Coll Cardiol 2022 Oct 4;80(14):1366-1418.

Ezetimibe

- **Mechanism of action:** Inhibits NPC1L1 protein; reduces cholesterol absorption in small intestine.
- **FDA-approved indication(s):** As adjunct to diet to: 1) ↓ TC, LDL-C, ApoB, non-HDL-C in patients with primary hyperlipidemia, either alone or in combination with statin therapy; 2) ↓ TC, LDL-C, ApoB, non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate; 3) ↓ TC, LDL-C with HoFH, in combination with atorvastatin or simvastatin; and 4) ↓ sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia)
- **Dose:** 10 mg orally daily, with or without food. Take either ≥2 h before or ≥4 h after BAS, if used in combination
- **Mean % reduction in LDL-C (per PI):** Monotherapy—18%; combination therapy with statin therapy (incremental reduction)—25%
- **Contraindication:** History of hypersensitivity to this medication.
- **Warnings/precautions:**
  1. Not recommended in patients with moderate/severe hepatic impairment.
  2. Persistent elevations in hepatic transaminases may occur with concomitant statin therapy. Monitor hepatic transaminases before and during treatment based on monitoring recommendations for statin therapy.
  3. Cases of myopathy and rhabdomyolysis have been reported when ezetimibe was used alone or in combination with statin therapy.
- **Adverse effects:** Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremities. In combination with statin—nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea
- **Use during pregnancy/lactation:** No safety data in humans; avoid use
- **Drug-drug interactions:** Cyclosporine, fibrates, BAS
- **CV outcomes trials:** IMPROVE-IT[8] (The addition of ezetimibe to moderate-intensity statin therapy in patients with recent ACS resulted in incremental lowering of LDL-C and reduced the primary composite endpoint of CV death, nonfatal MI, UA requiring rehospitalization, coronary revascularization [≥30 days after randomization], or nonfatal stroke. The median follow-up was 6 years); SHARP[35] (Simvastatin plus ezetimibe reduced LDL-C and reduced the primary endpoint of first major ASCVD event [nonfatal MI or CHD death, nonhemorrhagic stroke, or any arterial revascularization procedure] compared with placebo in patients with CKD over a median follow-up of 4.9 years)
- **Other prescribing considerations:** Generally well tolerated. Generic available

J Am Coll Cardiol 2022 Oct 4;80(14):1366-1418.

Ezetimibe

IMPROVE-IT (simvastatin + ezetimibe vs simvastatin + placebo)

- Patients ≥50 yo with hospitalization for ACS in the preceding 10 days
- >18,000 patients in 39 countries randomized
- Further LDL-C lowering (24%) with simvastatin + ezetimibe
- Primary end point: composite of death from CV disease, a major coronary event, or nonfatal stroke

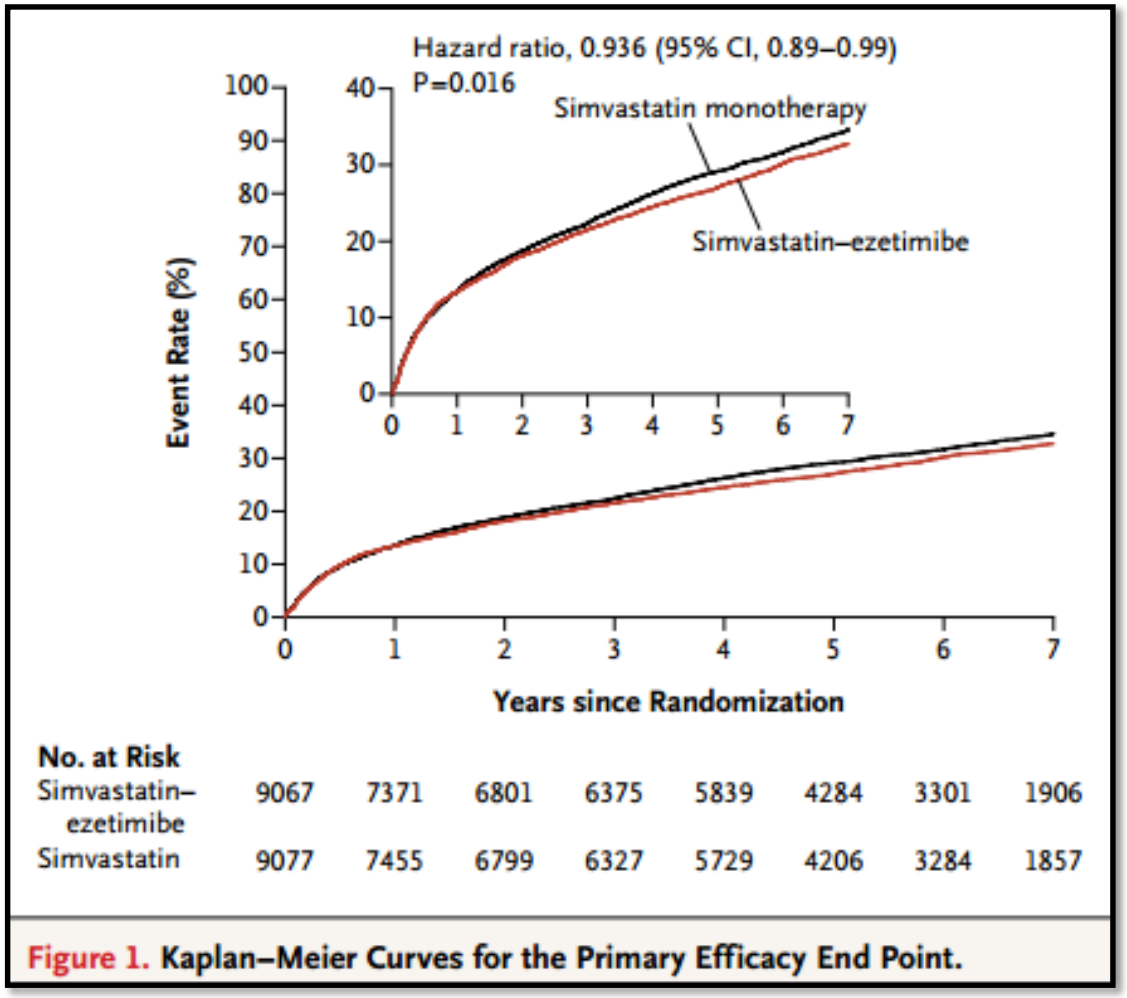


Figure 1. Kaplan–Meier Curves for the Primary Efficacy End Point.

New Engl J Med 2015;372(25):2387-97.

Bempedoic Acid

- **Mechanism of action:** ACL inhibitor; inhibits cholesterol synthesis in the liver; increases LDL receptor density. Bempedoic acid and its active metabolite require coenzyme A activation by ACSVL1, which is expressed primarily in the liver.
- **FDA-approved indication(s):** ↓ LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy.
- **Dose:** 180 mg orally once daily, with or without food.
- **Mean % reduction in LDL-C (per PI):** Combination therapy with statin therapy (placebo-corrected incremental reduction)—17%-18%.
- **Contraindication:** none
- **Warnings/precautions:** 1) May ↑ serum uric acid. Advise patients to contact their clinician if symptoms of hyperuricemia occur. Assess serum uric acid when clinically indicated. Monitor patients for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs, as appropriate. Assess uric acid level before initiation and if signs and symptoms of hyperuricemia occur. 2) Discontinue immediately if the patient experiences rupture of a tendon. Consider discontinuing if the patient experiences joint pain, swelling, or inflammation. Advise patients to rest at the first sign of tendinitis or tendon rupture and to contact their health care provider if tendinitis or tendon rupture symptoms occur. Consider alternative therapy in patients with a history of tendon disorders or tendon rupture.[17]
- **Adverse effects:** Upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes.
- **Use during pregnancy/lactation:** Discontinue when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus. There are no available data on use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.[17]
- **Drug-drug interactions:** Avoid concomitant simvastatin >20 mg daily or pravastatin >40 mg daily.
- **CV outcomes trials:** CV outcomes trials not completed. CLEAR Outcomes trial completion expected later in 2022.
- **Other prescribing considerations:** cost; pill burden; requires prior authorization

J Am Coll Cardiol 2022 Oct 4;80(14):1366-1418.

CLEAR Outcomes Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*

N Engl J Med 2023 Mar 4. doi: 10.1056/NEJMoa2215024.

CLEAR Outcomes Trial

The study enrolled 13,970 patients with high cardiovascular risk that were either unwilling or unable to take a statin

- mean age 65 years
- 48% women
- 91% white
- 70% with prior CV event

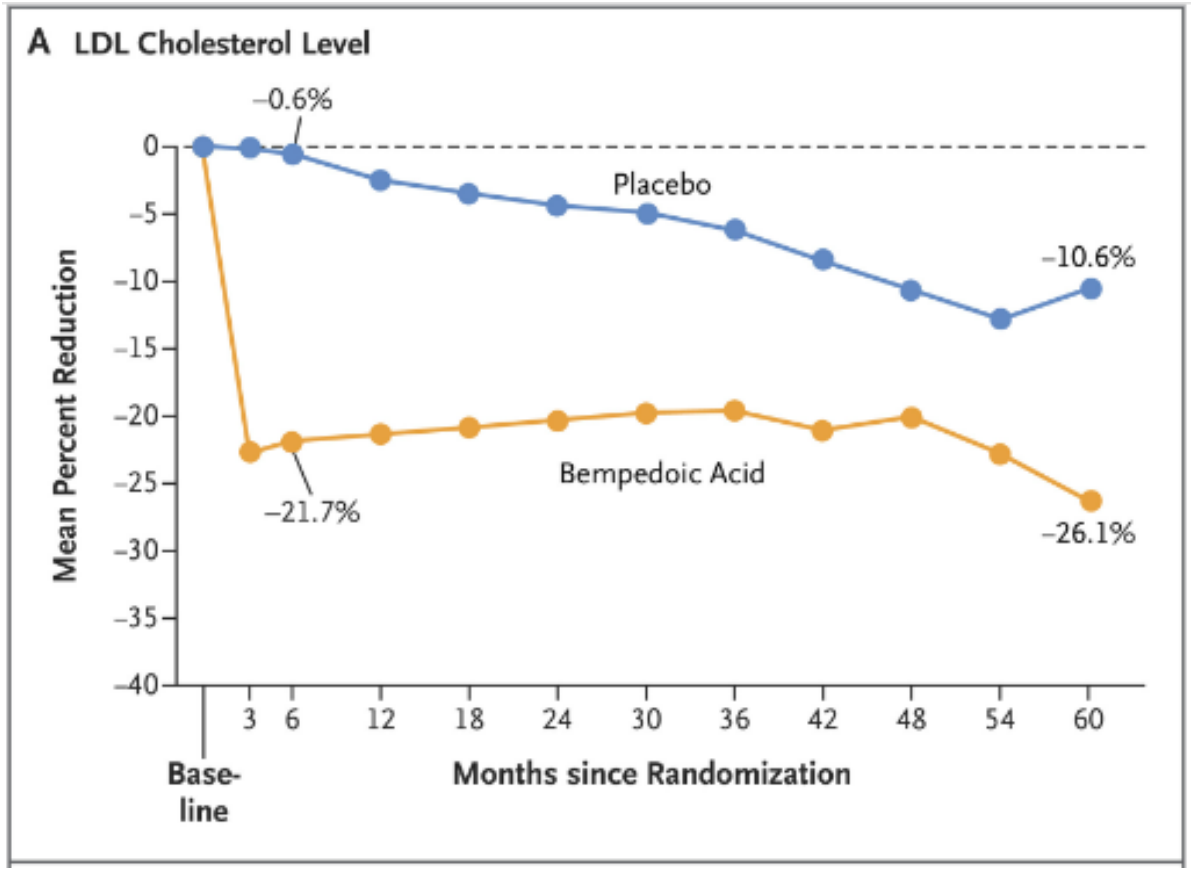
Randomized to either:

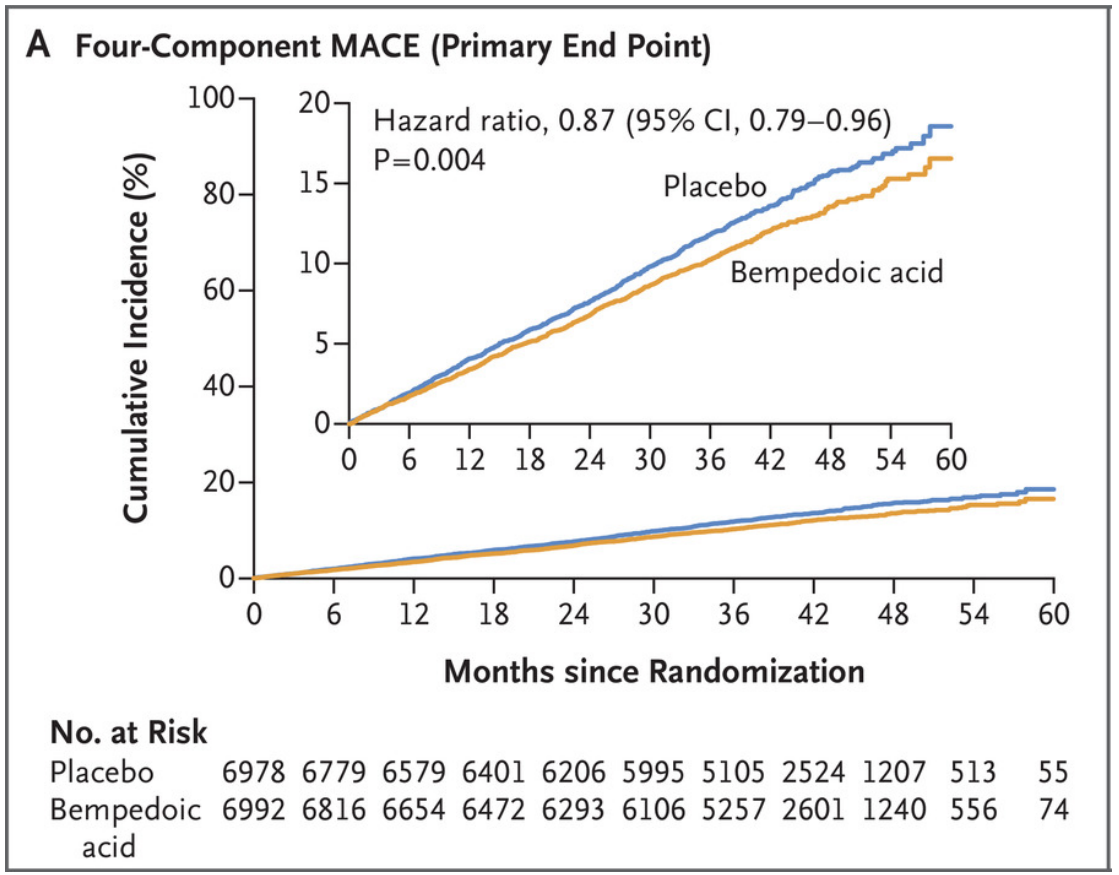
- Bempedoic Acid 180 mg PO daily
- Placebo PO daily

Primary Outcome: 4-point MACE (non-fatal MI, non-fatal stroke, CV revascularization, or CV death)

N Engl J Med 2023 Mar 4. doi: 10.1056/NEJMoa2215024.

CLEAR Outcomes Trial





N Engl J Med 2023 Mar 4. doi: 10.1056/NEJMoa2215024.

CLEAR Outcomes Trial

Take Home Point: Bempedoic Acid showed a modest absolute reduction in CV outcomes, relative to placebo, in patients "unable or unwilling" to take a statin.

- By 6 months, LDL-c had decreased by 21% more in the treatment group compared to placebo.
- At 3 year follow up, incidence of the primary composite endpoint (death from CV causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) was a 13% lower in the bempedoic acid group (p=0.004). Number needed to treat is 63.
- All-cause mortality was almost the same (about 6%) in the two groups, who had a similar frequency of serious adverse events (roughly 25%). Study-drug recipients experienced more hyperuricemia, gout, and renal impairment.

N Engl J Med 2023 Mar 4. doi: 10.1056/NEJMoa2215024.

Inclisiran

- **Mechanism of action:** siRNA targeting PCSK9; inhibits PCSK9 production in liver, thereby prolonging activity of LDL receptors.
- **FDA-approved indication(s):** ↓ LDL-C in adults with ASCVD or HeFH as adjunct to diet and maximally tolerated statin therapy.
- **Dose:** Administer 284 mg SC on day 1, day 90, and then every 6 months by a clinician.
- **Mean % reduction in LDL-C (per PI):** 48%-52%
- **Contraindications (per PI):** None
- **Warnings/precautions (per PI):** None
- **Adverse effects:** Injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremities, dyspnea
- **Use during pregnancy/lactation:** No safety data in humans; avoid use.
- **Drug-drug interactions (per PI):** None
- **CV outcomes trials:** CV outcomes trials not yet completed. ORION-4 currently in progress with estimated completion in 2026. VICTORION-2P currently in progress with estimated completion in 2027.
- **Other prescribing considerations:** robust LDL-C reduction, cost, requires SC administration by a clinician, requires prior authorization.

J Am Coll Cardiol 2022 Oct 4;80(14):1366-1418.

The NEW ENGLAND JOURNAL of MEDICINE

Inclisiran in Patients with Elevated LDL Cholesterol

TWO PHASE 3, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIALS

ORION-10
(U.S.)

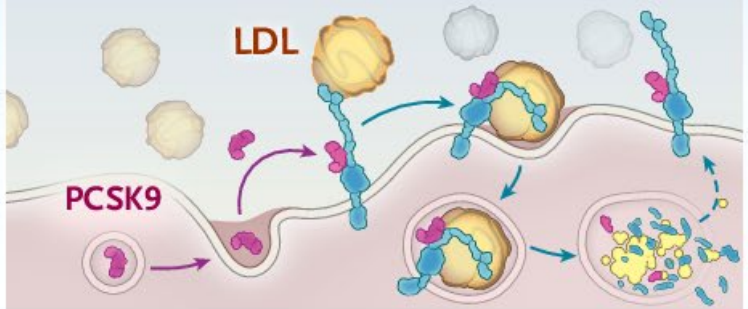
(N=1561)

–51.3% with Inclisiran

Difference, –52.3%
(95% CI, –55.7 to –48.8; P<0.001)

+1% with Placebo

Adults with CVD and elevated LDL



Percentage change in LDL cholesterol at 510 days

ORION-11
(Europe and South Africa)

(N=1617)

–45.8% with Inclisiran

Difference, –49.9%
(95% CI, –53.1 to –46.6; P<0.001)

+4% with Placebo

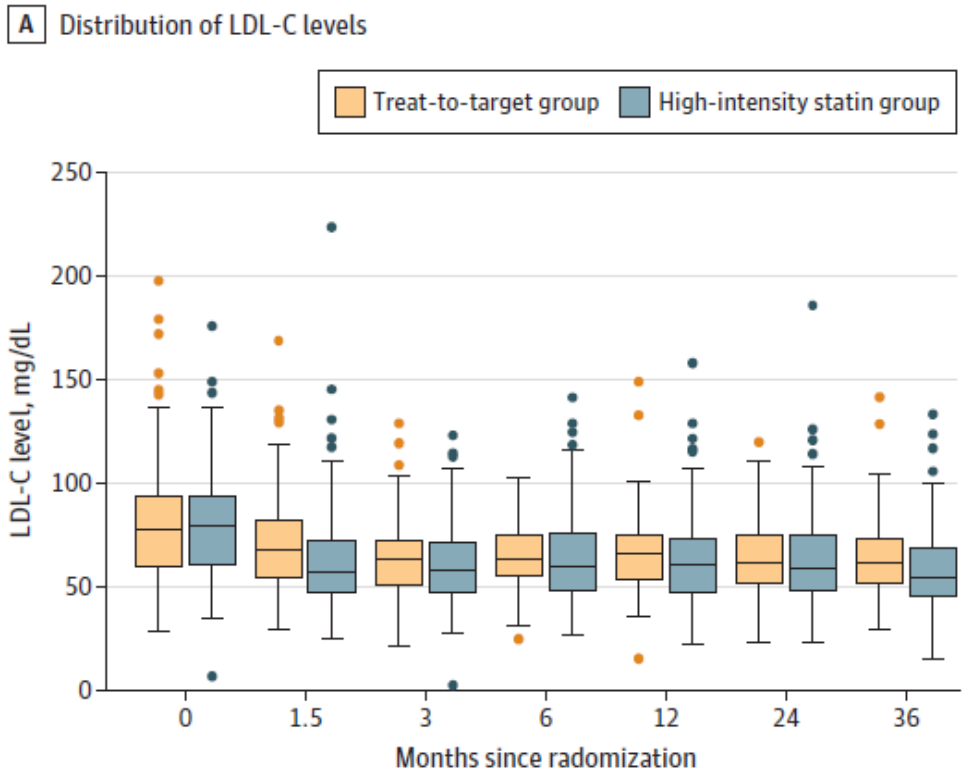
K.K. Ray et al. 10.1056/NEJMoa1912387

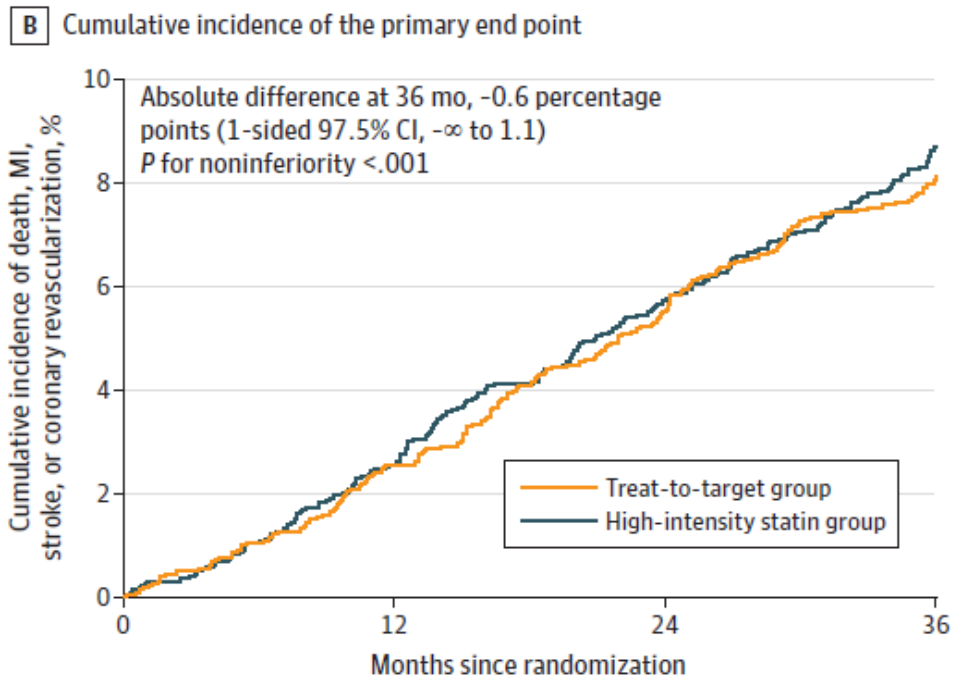
LODESTAR Study

JAMA | Original Investigation

Treat-to-Target or High-Intensity Statin in Patients With Coronary Artery Disease
A Randomized Clinical Trial

Sung-Jin Hong, MD; Yong-Joon Lee, MD; Seung-Jun Lee, MD; Bum-Kee Hong, MD; Woong Chol Kang, MD; Jong-Young Lee, MD; Jin-Bae Lee, MD; Tae-Hyun Yang, MD; Junghan Yoon, MD; Chul-Min Ahn, MD; Jung-Sun Kim, MD; Byeong-Keuk Kim, MD; Young-Guk Ko, MD; Donghoon Choi, MD; Yangsoo Jang, MD; Myeong-Ki Hong, MD; for the LODESTAR Investigators





JAMA 2023 Apr 4;329(13):1078-1087.

When poll is active, respond at **PollEv.com/levil606**

Text **LEVIL606** to **37607** once to join

Patient Case #2

TJ (our 62 yo male with diabetes, heart failure, CAD, and hypertension) returns to clinic after rechecking his labs recently, which showed: TC 175 mg/dL, HDL 45 mg/dL, LDL 78 mg/dL, and TG 140 mg/dL. He reports he has been adherent to his Rosuvastatin, which was optimized to 40 mg nightly 2 months ago after his last LDL resulted at 102 mg/dL.

What is the next appropriate therapy to consider for this patient to manage his cholesterol?

A. Increase Rosuvastatin to 80 mg nightly to target LDL < 70 mg/dL

B. Start Ezetimibe 10 mg daily to target LDL < 55 mg/dL

C. Start Bempedoic Acic 140 mg daily to target LDL < 70 mg/dL

D. No changes are needed; LDL is at goal of < 100 mg/dL

Summary

- Patients with very high CV risk should target an LDL-c < 55 mg/dL
- Patients with high CV risk should target an LDL-c < 70 mg/dL
- All other patients should target an LDL-c < 100 mg/dL
- After maximum tolerated statin, may consider treating with other non-statin therapies (Ezetimibe, Bempedoic Acid, Inclisiran, PSCK9 mAb, Bile Acid Sequestrant, Evinacumab, Lomitapide, or LDL Aphoresis)
- Treatment should always prioritize agents with proven CV benefit (Statins, Ezetimibe, Bempedoic Acid, PSCK9 mAb)

COPD Updates

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GOLD ABE Assessment Tool

Figure 2.3

Spirometrically confirmed diagnosis → Assessment of airflow obstruction → Assessment of symptoms/risk of exacerbations

Post-bronchodilator FEV1/FVC < 0.7

GRADE	FEV1 (% predicted)
GOLD 1	≥ 80
GOLD 2	50-79
GOLD 3	30-49
GOLD 4	< 30

EXACERBATION HISTORY (PER YEAR)

	SYMPTOMS: mMRC 0-1 CAT < 10	SYMPTOMS: mMRC ≥ 2 CAT ≥ 10
≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	E	E
0 or 1 moderate exacerbations (not leading to hospitalization)	A	B

CAT™ Assessment

Figure 2.2

For each item below, place a mark (x) in the box that best describes you currently.
Be sure to only select one response for each question.

EXAMPLE: I am very happy	0	1	2	3	4	5	I am very sad	Score
I never cough	0	1	2	3	4	5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0	1	2	3	4	5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0	1	2	3	4	5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0	1	2	3	4	5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0	1	2	3	4	5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0	1	2	3	4	5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0	1	2	3	4	5	I don't sleep soundly because of my lung condition	
I have lots of energy	0	1	2	3	4	5	I have no energy at all	

Reference: Jones et al. ERJ 2009; 34 (3); 648-54.

TOTAL SCORE:

LABA + LAMA

Previous Recommendation :

Group B: LABA or LAMA

Group C: LAMA

→ Group B and E: LAMA + LABA

New Recommendation:

Group B and E:

Treatment should be initiated with a LABA+LAMA combination. It has been shown in a RCT that in patients with ≤ 1 moderate exacerbation in the year before the study and a CAT ≥ 10 LABA+LAMA is superior to a LAMA regarding several endpoints.

No evidence to recommend one class of long- acting bronchodilators over another (LABA or LAMA) for initial relief of symptoms in this group of patients

Kew KM. Long-acting beta2-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2013.

EMAX Trial (2019)

LAMA/LABA (n=812) v LAMA monotherapy (n= 804) v LABA monotherapy (n=809)

Primary endpoint: FEV1 at 24 weeks

- LAMA/LABA v LAMA (56 mL) mono p<0.001
- LAMA/LABA v LABA mono (-19 mL) p <0.001

Secondary endpoint: transition dyspnoea Index at 24 weeks

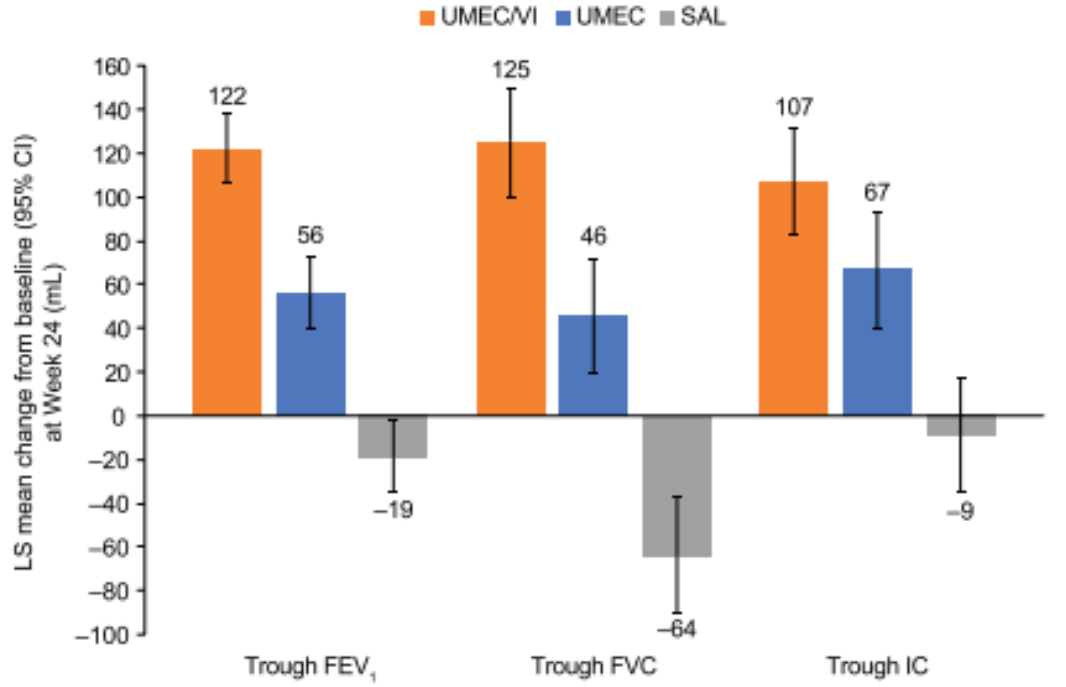
- Transition Dyspnoea Index: questionnaire assessing level of patient dyspnea
  - LAMA/LABA v LAMA mono p = 0.018
  - LAMA/LABA v LABA mono p= 0.004

Mean post-salbutamol FEV1: 55.4%

Mean CAT score at baseline: 19.2

Maltais F. Efficacy of umeclidinium/vilanterol versus umeclidinium and salmeterol monotherapies in symptomatic patients with COPD not receiving inhaled corticosteroids: the EMAX randomised trial. Respir Res 2019; 20(1): 238

EMAX Trial (2019)



	Difference (95% CI)		
UMEC/VI vs UMEC	66 mL (43, 89), $p < 0.001$	79 mL (42, 116), $p < 0.001$	41 mL (4, 77), $p = 0.028$
UMEC/VI vs SAL	141 mL (118, 164), $p < 0.001$	189 mL (152, 225), $p < 0.001$	116 mL (80, 152), $p < 0.001$

Fig. 2 Lung function outcomes. *CI*, confidence interval; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *IC*, inspiratory capacity; *LS*, least squares; *SAL*, salmeterol; *UMEC*, umeclidinium; *VI*, vilanterol

LAMA/LABA
Significant increase in FEV1, FVC, and IC

LAMA monotherapy
Greater improvement than LABA monotherapy in all three

LABA monotherapy
Inferior to LAMA or LAMA/LABA therapy

Respir Res 2019; 20(1): 238

Initial Pharmacological Treatment

Figure 4.2

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization

GROUP E

LABA + LAMA*

consider LABA+LAMA+ICS if blood eos ≥ 300*

0 or 1 moderate exacerbations (not leading to hospital admission)

GROUP A

A bronchodilator

mMRC 0-1, CAT < 10

GROUP B

LABA + LAMA*

mMRC ≥ 2, CAT ≥ 10

*single inhaler therapy may be more convenient and effective than multiple inhalers
Exacerbations refers to the number of exacerbations per year

Inhaled Corticosteroids

The Risk

Eosinophil Considerations:

Bafadhel (2018)

ICS/LABA (n=1436) v LABA monotherapy (n=1157) considering eos

Mean baseline eos: 170 cell/mL

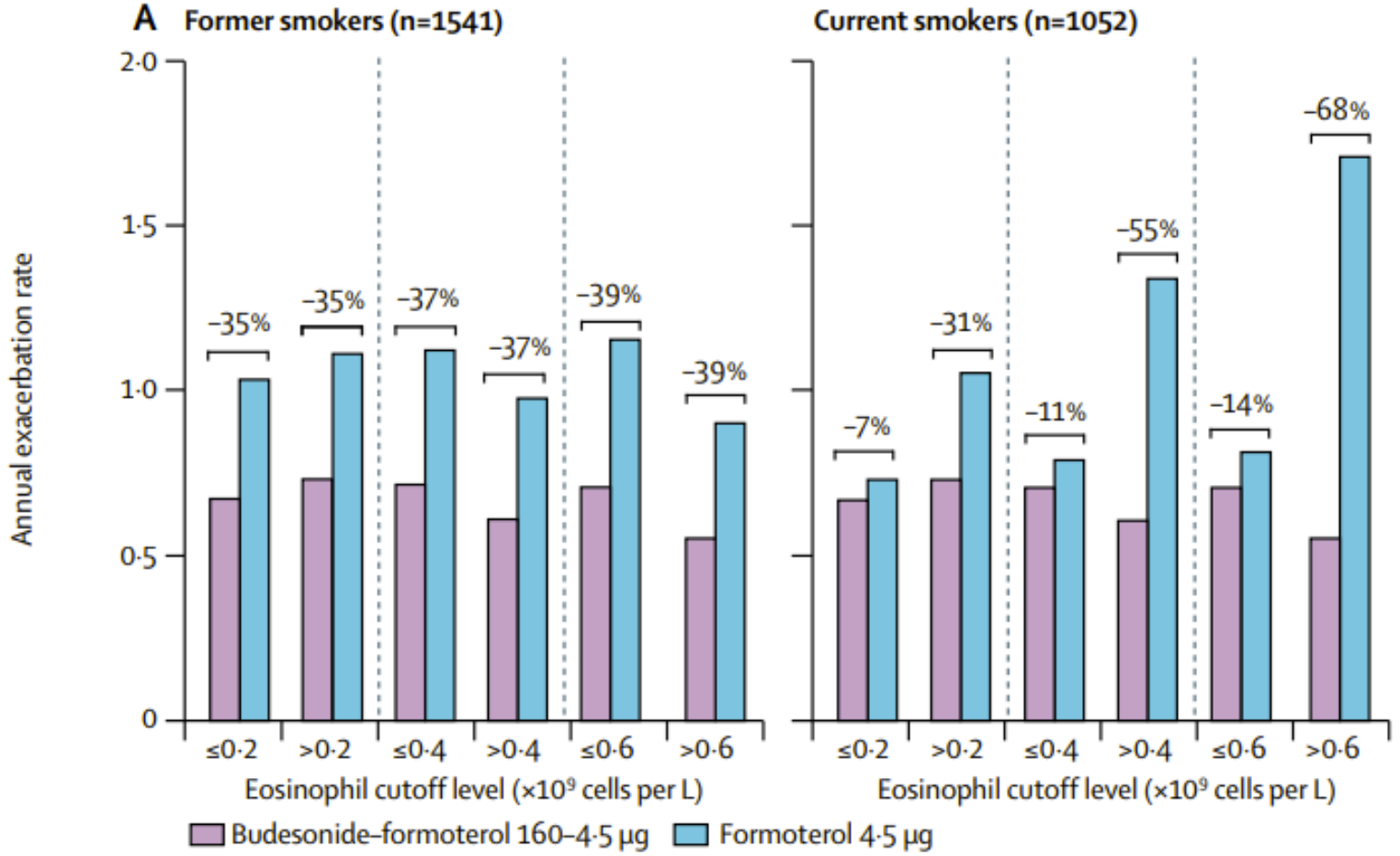
Results:

Eos <100 cells/µL : no change in exacerbation rates (p=0.47)

Eos >100 cells/µL : significant reduction in exacerbations rates in former smokers (p=0.013) compared to current smokers (p=0.0.15)

Lancet Respir Med 2018; 6(2): 117-26.

Inhaled Corticosteroids



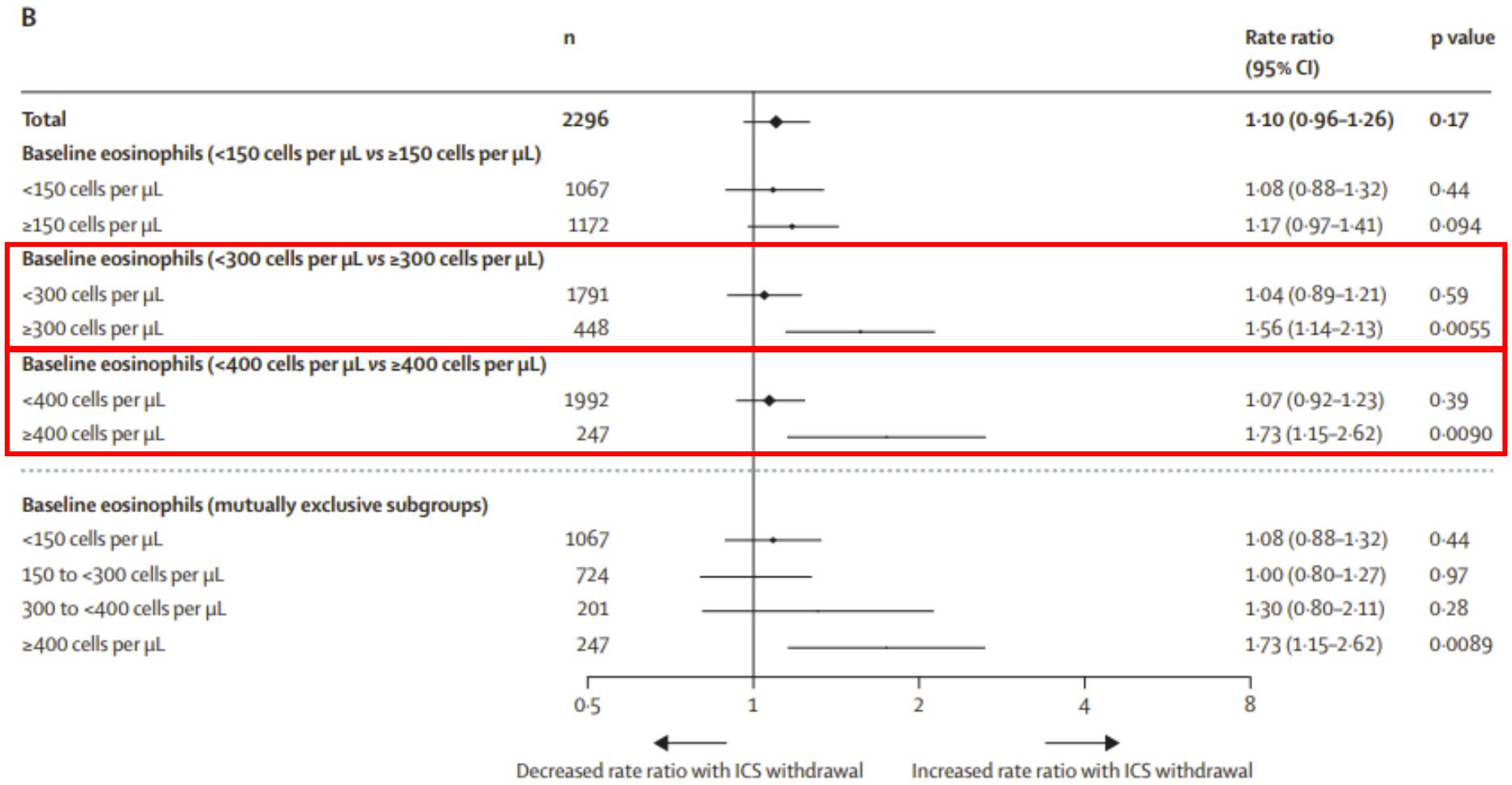
Lancet Respir Med 2018; 6(2): 117-26.

Inhaled Corticosteroids

- WISDOM Trial (2014) triple therapy with ICS tapering over 9 months
  - ICS continuation (n=1244) v ICS taper (n=1244) cohorts
  - ICS taper group significantly higher FEV1 reduction than ICS continuation group
    - At 18 weeks: p<0.001
    - At 52 weeks: p=0.001
  - Baseline eosinophil counts:
    - **≥ 150** cells/µL (n= 1275)
      - No significant change in exacerbation rate
    - **> 300** cells/µL **(n= 490)**
      - Increase in exacerbation rate (p= 0.024) with discontinuation
    - **>400** cells/µL **(n= 270)**
      - Increase in exacerbation rate (p= 0.029) with discontinuation

Lancet Respir Med. 2016 May;4(5):390-8.

Inhaled Corticosteroids? Should we?



Lancet Respir Med. 2016 May;4(5):390-8.

Factors to Consider when Initiating ICS Treatment

Figure 3.1

Factors to consider when adding ICS to long-acting bronchodilators:

(note the scenario is different when considering ICS withdrawal)

STRONGLY FAVORS USE	**History of hospitalization(s) for exacerbations of COPD[#]**
	≥ 2 moderate exacerbations of COPD per year[#]
	Blood eosinophils ≥ 300 cells/µL
	History of, or concomitant asthma
FAVORS USE	1 moderate exacerbation of COPD per year[#]
	Blood eosinophils 100 to < 300 cells/µL
AGAINST USE	**Repeated pneumonia events**
	Blood eosinophils < 100 cells/µL
	History of mycobacterial infection

[#]despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations); *note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

Adapted from & reproduced with permission of the © ERS 2019: *European Respiratory Journal 52 (6) 1801219; DOI: 10.1183/13993003.01219-2018 Published 13 December 2018*

Maintenance Therapy and Adjustments

DYSPNEA

LAMA or LABA

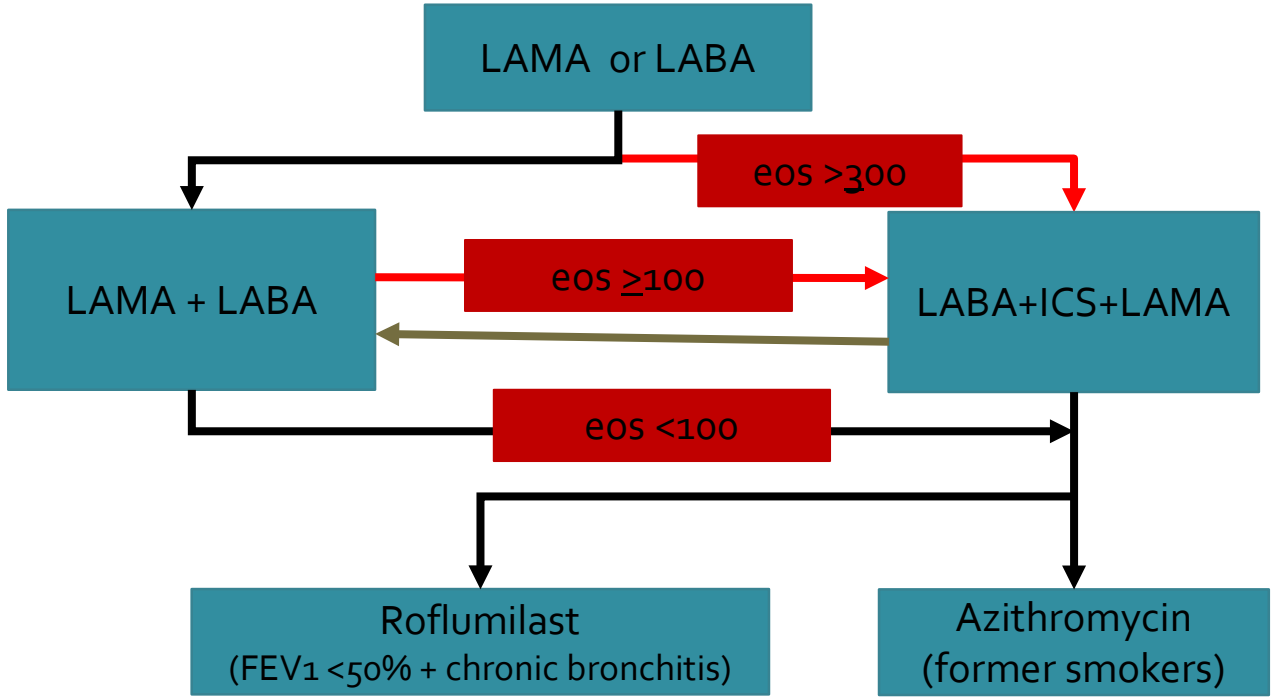
↓

LAMA + LABA

↓

- Consider switching inhalers
- Escalate non-pharmacological therapy
- Other causes of dyspnea

EXACERBATIONS



Consider de-escalation of ICS if:

- Pneumonia
- Inappropriate original classification
- Lack of response to ICS

Venkatesan P. GOLD COPD report: 2023 update. Lancet Respir Med. 2023 Jan

When poll is active, respond at **PollEv.com/levil606**

Text **LEVIL606** to **37607** once to join

Patient Case #3

RJ is a 54 y/o female with a PMH significant for HTN, urinary incontinence, and newly diagnosed COPD. She presents for a follow-up from her recent hospitalization 1 week ago for dyspnea. She was discharged on albuterol as needed and prednisone 20 mg daily x 5 days with plans to follow up with PCP to start maintenance therapy. CAT today was 22.

What is the best initial inhaler regimen for this patient?

A. Start Tiotropium 2 puffs daily

B. Start Tiotropium/Olodaterol 2 puffs daily

C. Start Formoterol/Budesonide 1 puff twice daily and as needed

D. Start Umeclidinium/Fluticasone/Vilanterol 1 puff daily

Spirometry *(today):*
FEV1 54%
FEV1/FVC ratio: 61%
after bronchodilation

Labs (*today*):
WBC 8
Hgb 13
Hct 32
Plts 213
Eos 75 cells/µL

Respiratory Treatments

2020

Allergy & Asthma Network

AllergyAsthmaNetwork.org

800.878.4403

American College of Allergy, Asthma & Immunology

CHEST FOUNDATION

= DOSE INDICATOR G = GENERIC AVAILABLE DISEASE STATES: A = ASTHMA C = COPD

Allergy & Asthma Network is a national nonprofit organization dedicated to ending needless death and suffering due to asthma, allergies and related conditions through outreach, education, advocacy and research.

SHORT-ACTING BETA$_2$-AGONIST BRONCHODILATORS

relax tight muscles in airways and offer quick relief of symptoms such as coughing, wheezing and shortness of breath for 3-6 hours

- **ProAir® Digihaler™** — 117 mcg albuterol sulfate — 1 2 3 A
- **ProAir® HFA** — 100 mcg albuterol sulfate — 1 2 3 A G
- **ProAir RespiClick®** — 117 mcg albuterol sulfate inhalation powder — 1 2 3 A
- **Proventil® HFA** — 120 mcg albuterol sulfate — 1 2 3 A
- **Ventolin® HFA** — 90 mcg albuterol sulfate — 1 2 3 A G
- **Xopenex HFA®** — 59 mcg levalbuterol tartrate — A G

LONG-ACTING BETA$_2$-AGONIST BRONCHODILATORS

relax tight muscles in airways and offer lasting relief of symptoms such as coughing, wheezing and shortness of breath for at least 12 hours

- **Arcapta™ Neohaler™** — 75 mcg indacaterol inhalation powder — C
- **Serevent® Diskus®** — 50 mcg salmeterol xinafoate inhalation powder — 1 2 3 A C
- **Striverdi® Respimat®** — 2.5 mcg olodaterol hydrochloride — 1 2 3 C

INHALED CORTICOSTEROIDS

reduce and prevent swelling of airway tissue; they do not relieve sudden symptoms of coughing, wheezing or shortness of breath

- **Alvesco® HFA** — 80, 160 mcg ciclesonide — 1 2 3 A
- **ArmonAir® Digihaler™** — 55, 113, 232 mcg fluticasone propionate inhalation powder — 1 2 3 A
- **ArmonAir® RespiClick®** — 55, 113, 232 mcg fluticasone propionate inhalation powder — 1 2 3 A
- **Arnuity® Ellipta®** — 50, 100, 200 mcg fluticasone furoate inhalation powder — 1 2 3 A
- **Asmanex® HFA** — 100, 200 mcg mometasone furoate — 1 2 3 A
- **Asmanex® Twisthaler®** — 110, 220 mcg mometasone furoate inhalation powder — 1 2 3 A
- **Flovent® Diskus®** — 50, 100, 250 mcg fluticasone propionate inhalation powder — 1 2 3 A
- **Flovent® HFA** — 44, 110, 220 mcg fluticasone propionate — 1 2 3 A
- **Pulmicort Flexhaler®** — 90, 180 mcg budesonide inhalation powder — 1 2 3 A
- **QVAR® Redihaler™** — 40, 80 mcg beclomethasone dipropionate — 1 2 3 A

COMBINATION MEDICATIONS

contain both inhaled corticosteroid and long-acting beta$_2$-agonist (LABA)

- **Advair Diskus®** — 100/50, 250/50, 500/50 mcg fluticasone propionate and salmeterol inhalation powder — 1 2 3 A C G
- **Advair® HFA** — 45/21, 115/21, 230/21 mcg fluticasone propionate and salmeterol xinafoate — 1 2 3 A G
- **AirDuo® Digihaler™** — 55/14, 113/14, 232/14 mcg fluticasone propionate and salmeterol inhalation powder — 1 2 3 A
- **AirDuo® RespiClick®** — 55/14, 113/14, 232/14 mcg fluticasone propionate and salmeterol inhalation powder — 1 2 3 A G
- **Breo® Ellipta®** — 100/25, 200/25 mcg fluticasone furoate and vilanterol inhalation powder — 1 2 3 A C
- **Dulera®** — 100/5, 200/5 mcg mometasone furoate and formoterol fumarate dihydrate — 1 2 3 A
- **Symbicort®** — 80/4.5, 160/4.5 mcg budesonide and formoterol fumarate dihydrate — 1 2 3 A C
- **Wixela™ Inhub™** — 100/50, 250/50, 500/50 mcg fluticasone propionate and salmeterol xinafoate (approved generic of Advair Diskus) — 1 2 3 A C

contain both long-acting beta$_2$-agonist (LABA) and long-acting muscarinic antagonist (LAMA)

- **Anoro® Ellipta®** — 62.5/25 mcg umeclidinium and vilanterol inhalation powder — 1 2 3 C
- **Bevespi Aerosphere®** — 9/4.8 mcg glycopyrrolate and formoterol fumarate — 1 2 3 C
- **Stiolto™ Respimat®** — 2.5/2.5 mcg tiotropium bromide and olodaterol — 1 2 3 C
- **Utibron™ Neohaler®** — 27.5/15.6 mcg indacaterol and glycopyrrolate inhalation powder — C

contains inhaled corticosteroid, long-acting beta$_2$-agonist (LABA) and long-acting muscarinic antagonist (LAMA)

- **Trelegy® Ellipta®** — 100/62.5/25 mcg fluticasone furoate, umeclidinium and vilanterol inhalation powder — 1 2 3 C

MUSCARINIC ANTAGONIST (ANTICHOLINERGIC)

relieve cough, sputum production, wheeze and chest tightness associated with chronic lung diseases

Short-acting

- **Atrovent® HFA** — 17 mcg ipratropium bromide — 1 2 3 C

Long-acting

- **Incruse® Ellipta®** — 62.5 mcg umeclidinium inhalation powder — 1 2 3 C
- **Seebri™ Neohaler®** — 15.6 mcg glycopyrrolate inhalation powder — C
- **Spiriva® HandiHaler®** — 18 mcg tiotropium bromide inhalation powder — C
- **Spiriva® Respimat®** — 1.25, 2.5 mcg tiotropium bromide — 1 2 3 A C
- **Tudorza™ Pressair™** — 400 mcg aclidinium bromide inhalation powder — 1 2 3 C

COMBINATION

muscarinic antagonist and beta$_2$-agonist

Short-acting

- **Combivent® Respimat®** — 20/100 mcg ipratropium bromide and albuterol — 1 2 3 C

Long-acting

- **Duaklir® Pressair®** — 400, 12 mcg aclidinium bromide and formoterol fumarate dihydrate — 1 2 3 C

BIOLOGICS

target cells and pathways that cause airway inflammation; delivered by injection or IV

- **Cinqair®** — reslizumab — A
- **Dupixent®** — dupilumab — A
- **Fasenra™** — benralizumab — A
- **Nucala®** — mepolizumab — A
- **Xolair®** — omalizumab — A

BRONCHIAL THERMOPLASTY

A minimally invasive procedure that uses mild heat to reduce airway smooth muscle, leading to fewer severe asthma flares, ER visits, and days lost from activities.
www.btforasthma.com

A

PDE4 INHIBITORS

ease lung inflammation and reduce exacerbations

- **Daliresp®** — 250, 500 mcg roflumilast — C

Reviewed by Dennis Williams, PharmD

COPD Summary

Transition previous recommendations for Groups C and D to Group E

In patients in Groups B and E use combination LAMA + LABA therapy

Initiate ICS at the appropriate time

- Eos >300 cells/µL at initiation
- Eos >100 cells/µL with increase in exacerbations

Discontinue ICS if increase in pneumonia infections

Thank you! Questions?

Clinical Guideline Update: What's new with Diabetes, Dyslipidemia, and COPD Management?

PLU Pharmacotherapeutic Update for Providers
May 6, 2023

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