New Drug Update 2021-2022

October 2022

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Faculty Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.
- I do not speak for or consult with any pharmaceutical manufacturer.

Use of Recombinant Zoster Vaccine in Immunocompromised Adults Aged ≥19 Years: MMWR / January 21, 2022 / Vol. 71 / No. 3 pp 80-84

- Dosing schedule. **Two RZV doses are necessary, regardless of previous history of herpes zoster or previous receipt of zoster vaccine live.** The **second RZV dose should typically be given 2–6 months after the first; for persons who are or will be immunodeficient or immunosuppressed and who would benefit from a shorter vaccination schedule, the second dose can be administered 1–2 months** after the first. If the second RZV dose is given sooner than 4 weeks after the first, a valid second dose should be repeated at least 4 weeks after the dose given too early. The vaccine **series does not need to be restarted if more than 6 months have elapsed since the first dose.**
- Timing of vaccination. **When possible, patients should be vaccinated before becoming immunosuppressed. Otherwise, providers should consider timing vaccination when the immune response is likely to be most robust** (i.e., during periods of lower immunosuppression and stable disease). RZV may be administered to patients who previously received varicella vaccine. RZV is not a live virus vaccine; therefore, **RZV may be administered while patients are taking antiviral medications.**
  - Concomitant administration of RZV with other adult vaccines has been studied, and there was no evidence for interference in the immune response to either vaccine or of safety concerns

Use of Recombinant Zoster Vaccine in Immunocompromised Adults Aged ≥19 Years: MMWR / January 21, 2022 / Vol. 71 / No. 3 pp 80-84

- **Pregnancy**. There is currently no ACIP recommendation for RZV use in pregnancy; therefore, **providers should consider delaying RZV until after pregnancy. There is no recommendation for pregnancy testing before vaccination.**
- **Breastfeeding**. Recombinant vaccines such as RZV pose no known risk to mothers who are breastfeeding or to their infants. Clinicians may **consider vaccination without regard to breastfeeding status if RZV is otherwise indicated.**
- Current episode of herpes zoster. RZV is not a treatment for herpes zoster or postherpetic neuralgia. **If a person is experiencing an episode of herpes zoster, vaccination should be delayed until the acute stage of the illness is over and symptoms abate.**

Universal Hepatitis B Vaccination in Adults ed 19–59 Years: Updated Recommendations of the ACIP

MMWR / April 1, 2022 / 71(13);477–483

- **Recommendations - HepB vaccination is recommended for all adults aged 19–59 years and adults aged ≥60 years with risk factors for hepatitis B. Adults aged ≥60 years without known risk factors for hepatitis B may also receive HepB vaccines**. Infants and all other persons aged <19 years are already recommended to receive HepB vaccines.
  - Rates of reported acute hepatitis B have not notably decreased for over 1 decade, with 20,700 estimated infections in 2019.
  - The safety of single-antigen 3-dose HepB vaccines has been established. Pre-Hevbrio was approved by FDA in 2021 and recommended by ACIP in 2022. Little or no difference in seroprotection or occurrence of serious adverse events or mild adverse events (GRADE evidence type 3; low certainty evidence) was found for PreHevbrio in comparison with a 3-dose, single-antigen vaccine (Engerix-B), and serious adverse events were rare for both vaccines. The 2-dose HepB vaccine (Heplisav-B) was approved by FDA in 2017 and recommended by ACIP in 2018. No difference in occurrence of serious adverse events (GRADE evidence type 1; high certainty evidence) was found for Heplisav-B compared with a 3-dose vaccine (Engerix-B), and serious adverse events were rare for both vaccines.

Updated Recommendations of the Advisory Committee on Immunization Practices — MMWR / January 28, 2022 / 71(4);109–117

New Pneumococcal Vaccine Recommendations

- **Adults aged ≥65 years who have not previously received PCV or whose previous vaccination history is unknown should receive 1 dose of PCV (either PCV20 or PCV15). When PCV15 is used, it should be followed by a dose of PPSV23.**
- **Adults aged 19–64 years with certain underlying medical conditions or other risk factors who have not previously received PCV or whose previous vaccination history is unknown should receive 1 dose of PCV (either PCV20 or PCV15). When PCV15 is used, it should be followed by a dose of PPSV23.**
  - **When PCV15 is used, the recommended interval between administration of PCV15 and PPSV23 is ≥1 year. A minimum interval of 8 weeks can be considered for adults with an immunocompromising condition,** cochlear implant, or cerebrospinal fluid leak to minimize the risk for IPD caused by serotypes unique to PPSV23 in these vulnerable groups.

Updated Recommendations of the Advisory Committee on Immunization Practices — MMWR / January 28, 2022 / 71(4);109–117

- **Adults who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose. When PCV15 is used in those with history of PPSV23 receipt, it need not be followed by another dose of PPSV23.**
- **Adults with previous PCV13. The incremental public health benefits of providing PCV15 or PCV20 to adults who have received PCV13 only or both PCV13 and PPSV23 have not been evaluated. These adults should complete the previously recommended PPSV23.**
  - Coadministration with other vaccines. PCV15, PCV20, or PPSV23 can be coadministered with QIV in an adult immunization program, as **concomitant administration (PCV15 or PPSV23 and QIV [Fluarix], PCV20 and adjuvanted QIV [Fluad]) has been demonstrated to be immunogenic and safe**. However, slightly lower pneumococcal serotype-specific OPA GMTs or geometric mean concentrations were reported when pneumococcal vaccines were coadministered with QIV compared with when pneumococcal vaccines were given alone. Currently, no data are available on coadministration with other vaccines (e.g., tetanus, diphtheria, acellular pertussis vaccine, hepatitis B, or zoster vaccine) among adults. **Evaluation of coadministration of PCV15, PCV20, or PPSV23 with COVID-19 vaccines is ongoing.**

TABLE 1. Recommendations for use of 15-valent pneumococcal conjugate vaccine in series with 23-valent pneumococcal polysaccharide vaccine or 20-valent pneumococcal conjugate vaccine in pneumococcal conjugate vaccine-naïve adults aged ≥19 years — United States, 2022

Medical indication group	Specific underlying medical condition	Age group, yrs	
		19–64	≥65
None	None	None	1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥1 years later*
Underlying medical conditions or other risk factors	Alcoholism Chronic heart disease† Chronic liver disease Chronic lung disease¶ Cigarette smoking Diabetes mellitus Cochlear implant CSF leak Congenital or acquired asplenia Sickle cell disease or other hemoglobinopathies Chronic renal failure** Congenital or acquired immunodeficiencies**,†† Generalized malignancy** HIV infection** Hodgkin disease** Iatrogenic immunosuppression**,§§ Leukemia** Lymphoma** Multiple myeloma** Nephrotic syndrome** Solid organ transplant**	1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥1 years later§	1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥1 years later*

ACIP* recommends 15-valent pneumococcal conjugate vaccine (PCV15) as an option for pneumococcal conjugate vaccination of children**

- PCV13 and PCV15:
  - can be used interchangeably
  - are recommended for all children aged 2–59 months and some others based on risk factors
  - can be administered at the same time as other routine vaccines, including COVID-19, using different syringes and vaccine sites
- PCV15 can be used according to currently recommended PCV13 dosing and schedules

Make sure your patients are up to date with their pneumococcal vaccinations

* ACIP (Advisory Committee on Immunization Practices)

** Risk-based recommendations on use of PPSV23 for people aged 2–18 years with certain underlying medical conditions that increase the risk for pneumococcal disease have not changed.

bit.ly/mm7137a3

SEPTEMBER 22, 2022

MMWR

ACIP Meeting 6/22-23/2022

- The **committee voted 15-0 to recommend that people aged 65 years or older receive a high-dose inactivated influenza vaccine, adjuvanted inactivated influenza vaccine, or recombinant influenza vaccine over any of the standard-dose unadjuvanted, inactivated vaccines.**
- **The committee also voted unanimously to recommend Vaxneuvance (PCV15) for children. Merck's 15-valent pneumococcal vaccine was approved by the FDA for infants and children aged 6 weeks to 17 years.**
    - **The immune responses elicited by PCV15 following a four-dose pediatric series were noninferior to the currently available 13-valent pneumococcal conjugate vaccine (PCV13). They determined that both vaccines will be recommended as a 4-dose series at 2, 4, 6, and 12 to 15 months and that the two can be used interchangeably.**
- **The committee gave the green light to a second MMR vaccine, Priorix (GSK), for use as an option in the U.S. in people aged 6 months or older. Previously, only Merck's MMR vaccine was available.**

At-a-Glance

COVID-19 Vaccination Schedule for Most People

(People who are NOT Moderately or Severely Immunocompromised)

People ages 6 months through 4 years

Moderna

Primary → (In 4-8 weeks) → Primary

-OR-

Pfizer-BioNTech

Primary → (In 3-8 weeks) → Primary → (In at least 8 weeks) → Primary

People ages 5 through 11 years

Moderna

Primary → (In 4-8 weeks) → Primary

-OR-

Pfizer-BioNTech

Primary → (In 3-8 weeks) → Primary → (In at least 5 months) → Monovalent Booster

People ages 12 years and older

Moderna, Novavax, or Pfizer-BioNTech

Primary → (In 3-8 weeks (Novavax, Pfizer) / or in 4-8 weeks (Moderna)) → Primary → (In at least 2 months) → Bivalent booster*

People ages 18 years and older who previously received Janssen primary series dose†

Primary → (In at least 2 months) → Bivalent booster*

For more specific clinical guidance, see:

- Pre-exposure prophylaxis
- Interim COVID-19 Immunization Schedule
- Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States

Note: This schedule does not include clinical details necessary for administering COVID-19 vaccines. For clinical details, see the resources at the end of this document.

* The bivalent booster dose is administered at least 2 months after completion of the primary series. For people who previously received a monovalent booster dose(s), the bivalent booster dose is administered at least 2 months after the last monovalent booster dose.

† Janssen COVID-19 Vaccine should only be used in certain limited situations. See: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us-appendix.html#appendix-a

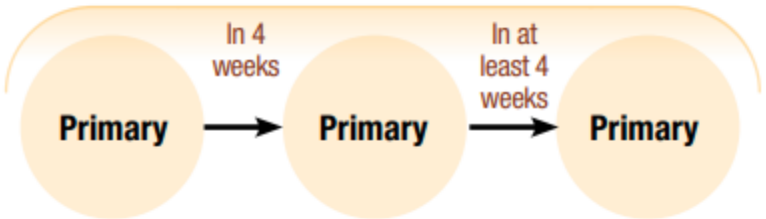
CS 333881-A | 09/06/2022

At-a-Glance

COVID-19 Vaccination Schedule for People Who Are Moderately or Severely Immunocompromised

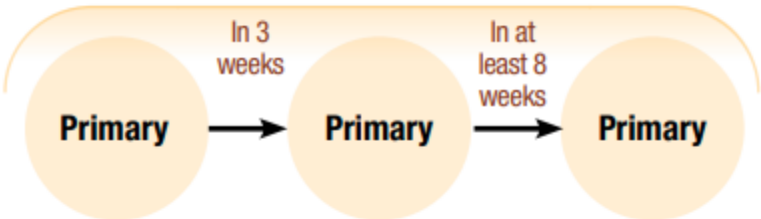
People ages 6 months through 4 years

Moderna



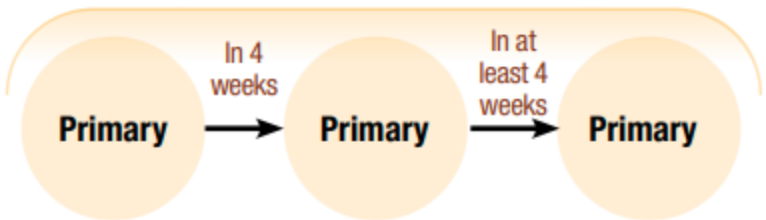
-OR-

Pfizer-BioNTech



People ages 5 years through 11 years

Moderna



-OR-

Pfizer-BioNTech

For more specific clinical guidance, see:

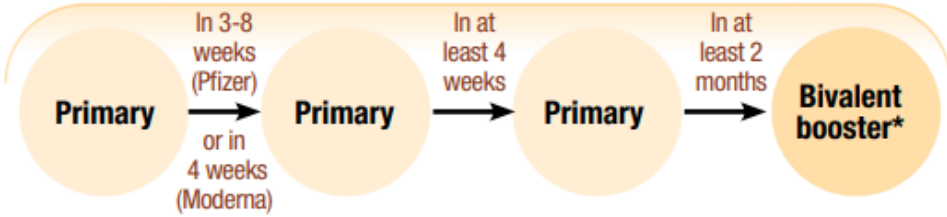
- Pre-exposure prophylaxis
- Interim COVID-19 Immunization Schedule
- Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States

At-a-Glance

COVID-19 Vaccination Schedule for People Who Are Moderately or Severely Immunocompromised

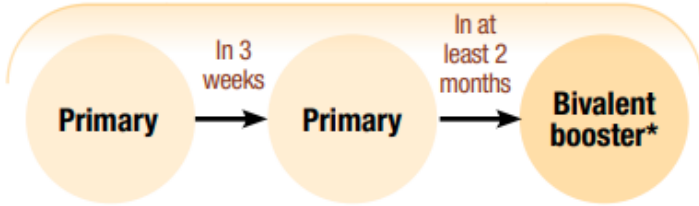
People ages 12 years and older

Moderna or Pfizer-BioNTech

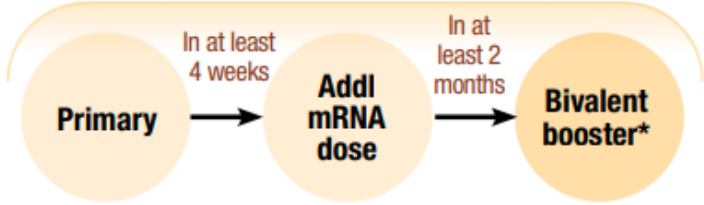


-OR-

Novavax



People ages 18 years and older who previously received Janssen primary series dose†

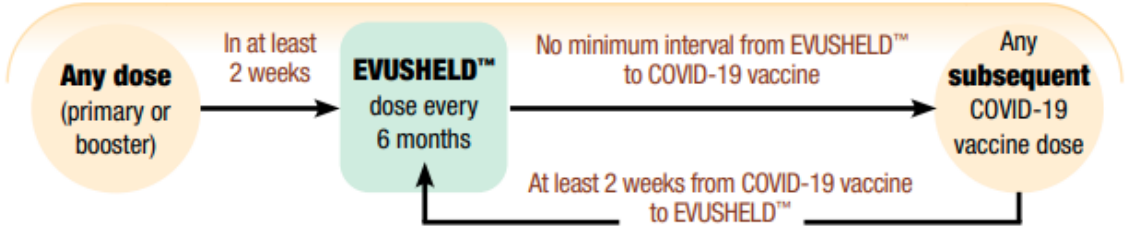


For more specific clinical guidance, see:

- Pre-exposure prophylaxis
- Interim COVID-19 Immunization Schedule
- Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States

Monoclonal antibodies (EVUSHELD™) for COVID-19 pre-exposure prophylaxis

People ages 12 years and older (must weigh at least 40kg)



Note: This schedule does not include clinical details necessary for administering COVID-19 vaccines. For clinical details, see the resources at the end of this document.

* The bivalent booster dose is administered at least 2 months after completion of the primary series. For people who previously received a monovalent booster dose(s), the bivalent booster dose is administered at least 2 months after the last monovalent booster dose.

† Janssen COVID-19 Vaccine should only be used in certain limited situations. See: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us-appendix.html#appendix-a

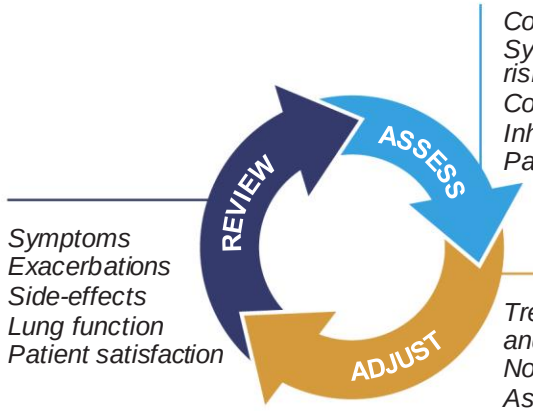
CS 333881-A | 09/06/2022

Global Initiative for Asthma (GINA)
What's new in GINA 2022?

GINA Global Strategy for Asthma Management and Prevention

Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications (adjust down/up/between tracks)
Education & skills training

CONTROLLER and **PREFERRED RELIEVER** (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP
RELIEVER: As-needed low-dose ICS-formoterol			

See GINA severe asthma guide

NOTE ICS-formoterol is NOT FDA Approved for this indication

CONTROLLER and **ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP
RELIEVER: As-needed short-acting beta$_2$-agonist				

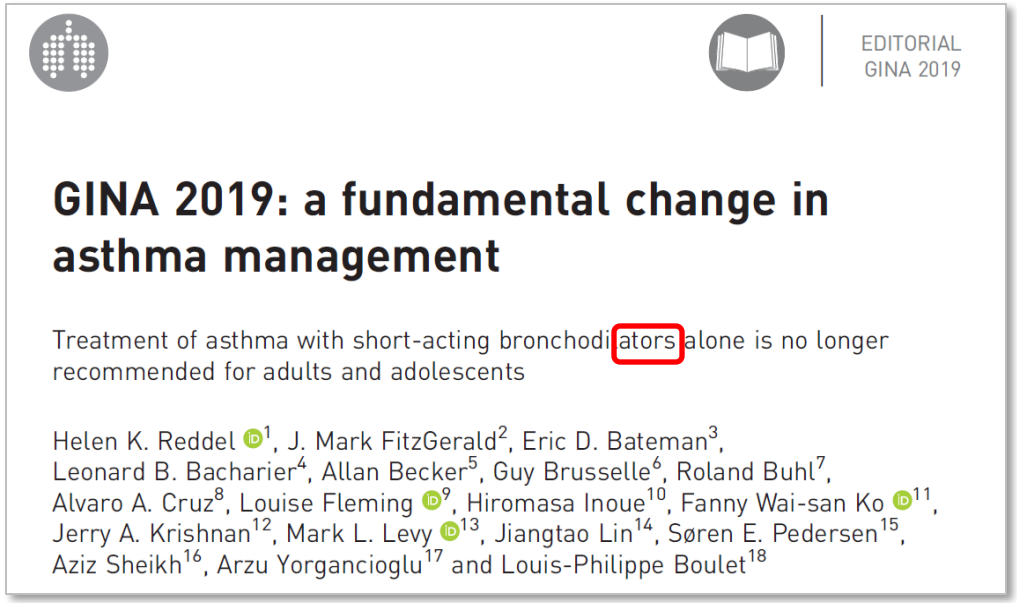
Other controller options for either track (limited indications, or less evidence for efficacy or safety)	*Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT*	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

GINA treatment figure for adults and adolescents (≥12 years)

- Treatment options are shown in two tracks
  - This was necessary to clarify how to step treatment up and down with the same reliever
- Track 1, with low dose ICS-formoterol as the reliever, is the preferred strategy
  - Preferred because of the evidence that using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever, with similar symptom control and lung function
- Track 2, with SABA as the reliever, is an 'alternative' (non-preferred) strategy
  - Less effective than Track 1 for reducing severe exacerbations
  - Use Track 2 if Track 1 is not possible; can also consider Track 2 if a patient has good adherence with their controller, and has had no exacerbations in the last 12 months
  - Before considering a regimen with SABA reliever, consider whether the patient is likely to continue to be adherent with daily controller – if not, they will be exposed to the risks of SABA-only treatment
- "Other controller options"
  - These have limited indications, or less evidence for efficacy and/or safety than Track 1 or 2 options
- Step 5
  - A new class of biologic therapy has been added (anti-TSLP)
  - A prompt added about the GINA severe asthma guide

Why not treat with SABA alone?

- Inhaled SABA has been first-line treatment for asthma for 50 years
  - Asthma was thought to be a disease of bronchoconstriction
  - Role of SABA reinforced by rapid relief of symptoms and low cost
- **Regular use of SABA, even for 1–2 weeks, is associated with increased airway hyperresponsiveness , reduced bronchodilator effect, increased allergic response, increased eosinophils** (e.g. Hancox, 2000; Aldridge, 2000)
  - Can lead to a vicious cycle encouraging overuse
  - Over-use of SABA associated with ↑ exacerbations and ↑ mortality (e.g. Suissa 1994, Nwaru 2020)
- Starting treatment with SABA trains the patient to regard it as their primary asthma treatment
- The only previous option was daily ICS even when no symptoms, but adherence is extremely poor
- GINA changed its recommendation once evidence for a safe and effective alternative was available


EDITORIAL
GINA 2019

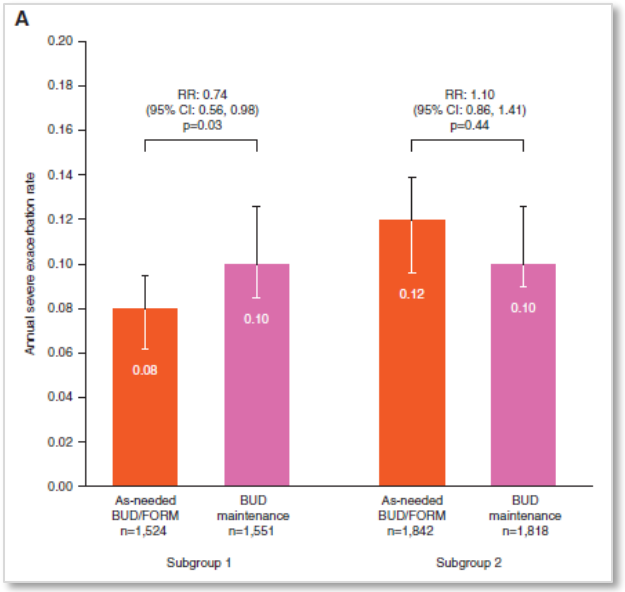
GINA 2019: a fundamental change in asthma management

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

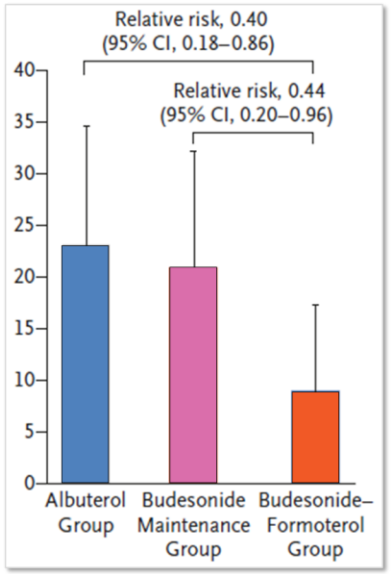
Helen K. Reddel[1], J. Mark FitzGerald[2], Eric D. Bateman[3], Leonard B. Bacharier[4], Allan Becker[5], Guy Brusselle[6], Roland Buhl[7], Alvaro A. Cruz[8], Louise Fleming[9], Hiromasa Inoue[10], Fanny Wai-san Ko[11], Jerry A. Krishnan[12], Mark L. Levy[13], Jiangtao Lin[14], Søren E. Pedersen[15], Aziz Sheikh[16], Arzu Yorgancioglu[17] and Louis-Philippe Boulet[18]

New evidence for as-needed ICS-formoterol in mild asthma

- **Meta-analysis of four all RCTs, n=9,565**
  (Crossingham, Cochrane 2021)
  - **55% reduction in severe exacerbations compared with SABA alone**
  - **Similar risk of severe exacerbations as with daily ICS + as-needed SABA**
  - **ED visits or hospitalizations**
    - **65% lower than with SABA alone**
    - **37% lower than with daily ICS**
- Analysis by previous treatment
  - Patients taking SABA alone had lower risk of severe exacerbations with as-needed ICS-formoterol compared with daily ICS + as-needed SABA *(Bateman, Annals ATS 2021; Beasley, NEJMed 2019)*



Bateman 2021



Beasley 2019

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD):

TEACHING SLIDE SET 2022

This slide set is restricted for academic and educational purposes only.
Use of the slide set, or of individual slides, for commercial or promotional purposes requires approval from GOLD.

BRONCHODILATORS IN STABLE COPD

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**.
- Regular and as-needed use of SABA or SAMA improves FEV_1 and symptoms **(Evidence A)**.
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms **(Evidence A)**. **IE. albuterol/ipratropium - Combivent vs. albuterol**
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**.
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**.
- Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy **(Evidence A)**. **Umeclidinium/ Vilanterol (Anoro®), Tiotropium/Olodaterol (Stiolto®) QD Glycopyrrolate/Formoterol (Bevespi®) and Glycopyrronium/Indacaterol (Ultibron®) BID**
- Combination treatment with a LABA/LAMA reduces exacerbations compared to monotherapy **(Evidence B)**.
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance **(Evidence B)**.
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**.

FACTORS TO CONSIDER WHEN INITIATING ICS TREATMENT

Factors to consider when initiating ICS treatment in combination with one or two long-acting bronchodilators (note the scenario is different when considering ICS withdrawal):

· STRONG SUPPORT ·	· CONSIDER USE ·	· AGAINST USE ·
• History of hospitalization(s) for exacerbations of COPD#	• 1 moderate exacerbation of COPD per year#	• Repeated pneumonia events
• ≥ 2 moderate exacerbations of COPD per year#	• Blood eosinophils ≥ 100 to < 300 cells/µL	• Blood eosinophils <100 cells/µL
• Blood eosinophils ≥ 300 cells/µL		• History of mycobacterial infection
• History of, or concomitant, asthma		

#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.

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

FIGURE 3.1

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Developed in partnership with the Heart Failure Society of America

https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063
https://www.jacc.org/doi/10.1016/j.jacc.2021.12.012
https://www.onlinejcf.com/article/S1071-9164(22)00076-8/fulltext

Revised Classification of HF by LVEF

HFrEF	HFimpEF	HFmrEF	HFpEF
• LVEF ≤40%	• Previous LVEF ≤40% and follow-up measurement of LVEF >40%	• LVEF 41-49%	• LVEF ≥50%

Evidence of spontaneous or provokable increase LV filling pressures (e.g., elevated NP, noninvasive and invasive hemodynamic measurement)

J Cardiac Fail 2021;27:387-413 | Circulation. 2022;145:00–00. DOI: 10.1161/CIR.0000000000001063

HFrEF Quadruple Treatment

ARNi

- Recommended in NYHA II-III to reduce M&M — 1 A
- Replace ACEi or ARB with ARNI in NYHA II-III — 1 B-R
- ACEi is beneficial to reduce M&M when ARNi not feasible — 1 A

BB

- Metoprolol succinate, carvedilol, or bisoprolol recommended to reduce mortality & hospitalizations

1 A

MRA

- Recommended in NYHA II-IV to reduce M&M, if eGFR >30 mL/min/1.73m^2 and serum K <5 mEq/L

1 A

SGLT2i

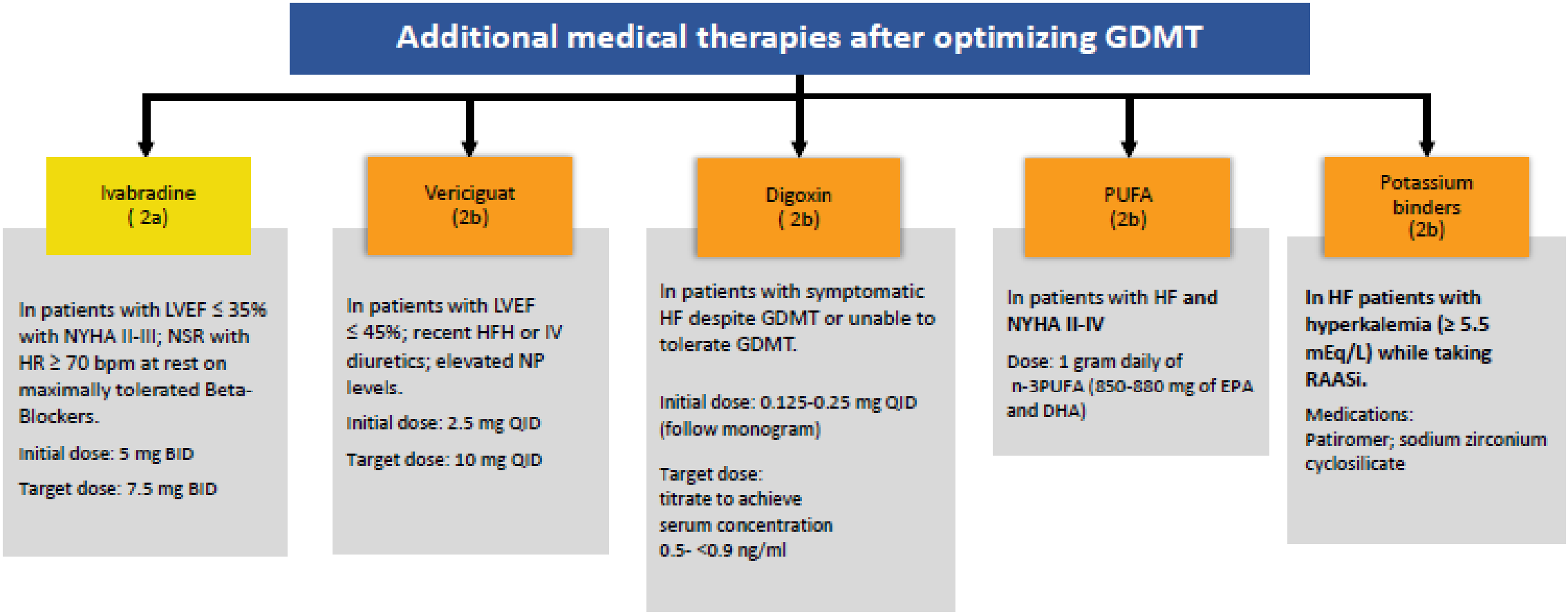
- Recommended to reduce HHF and CV mortality, irrespective of the presence of T2DM

1 A

CV, cardiovascular; HHF, hospitalization for HF; M&M, morbidity & mortality; T2DM, type 2 diabetes

Circulation. 2022;145:00–00. DOI: 10.1161/CIR.0000000000001063

Additional Therapies After GDMT Optimization



Circulation. 2022;145:00–00. DOI: 10.1161/CIR.0000000000001063

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

https://www.jacc.org/doi/10.1016/j.jacc.2021.12.012

TABLE 14 Drugs Commonly Used for HFrEF (Stage C HF)

Drug	Initial Daily Dose(s)	Target Doses(s)	Mean Doses Achieved in Clinical Trials	References
ACEi				
Captopril	6.25 mg 3 times daily	50 mg 3 times daily	122.7 mg total daily	(19)
Enalapril	2.5 mg twice daily	10–20 mg twice daily	16.6 mg total daily	(3)
Fosinopril	5–10 mg once daily	40 mg once daily	NA	...
Lisinopril	2.5–5 mg once daily	20–40 mg once daily	32.5–35.0 mg total daily	(17)
Perindopril	2 mg once daily	8–16 mg once daily	NA	...
Quinapril	5 mg twice daily	20 mg twice daily	NA	...
Ramipril	1.25–2.5 mg once daily	10 mg once daily	NA	...
Trandolapril	1 mg once daily	4 mg once daily	NA	...
ARB				
Candesartan	4–8 mg once daily	32 mg once daily	24 mg total daily	(20)
Losartan	25–50 mg once daily	50–150 mg once daily	129 mg total daily	(18)
Valsartan	20–40 mg once daily	160 mg twice daily	254 mg total daily	(21)
ARNi				
Sacubitril-valsartan	49 mg sacubitril and 51 mg valsartan twice daily (therapy may be initiated at 24 mg sacubitril and 26 mg valsartan twice daily)	97 mg sacubitril and 103 mg valsartan twice daily	182 mg sacubitril and 193 mg valsartan total daily	(22)
Beta blockers				
Bisoprolol	1.25 mg once daily	10 mg once daily	8.6 mg total daily	(1)
Carvedilol	3.125 mg twice daily	25–50 mg twice daily	37 mg total daily	(23)
Carvedilol CR	10 mg once daily	80 mg once daily	NA	...
Metoprolol succinate extended release (metoprolol CR/XL)	12.5–25 mg once daily	200 mg once daily	159 mg total daily	(11)

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Mineralocorticoid receptor antagonists				
Spironolactone	12.5–25 mg once daily	25–50 mg once daily	26 mg total daily	(6)
Eplerenone	25 mg once daily	50 mg once daily	42.6 mg total daily	(13)
SGLT2i				
Dapagliflozin	10 mg once daily	10 mg once daily	9.8 mg total daily	(8)
Empagliflozin	10 mg once daily	10 mg once daily	NR	(9)
Isosorbide dinitrate and hydralazine				
Fixed dose combination	20 mg isosorbide dinitrate and 37.5 mg hydralazine 3 times daily	40 mg isosorbide dinitrate and 75 mg hydralazine 3 times daily	90 mg isosorbide dinitrate and ~175 mg hydralazine total daily	(10)
Isosorbide dinitrate and hydralazine	20–30 mg isosorbide dinitrate and 25–50 mg hydralazine 3–4 times daily	120 mg isosorbide dinitrate total daily in divided doses and 300 mg hydralazine total daily in divided doses	NA	(24)
I_f Channel inhibitor				
Ivabradine	5 mg twice daily	7.5 mg twice daily	12.8 total daily	(25–27)
Soluble guanylate cyclase stimulator				
Vericiguat	2.5 mg once daily	10 mg once daily	9.2 mg total daily	(28)
Digoxin	0.125–0.25 mg daily (modified according to monogram)	Individualized variable dose to achieve serum digoxin concentration 0.5–<0.9 ng/mL	NA	(29,30)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CR, controlled release; CR/XL, controlled release/extended release; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NA, not applicable; NR, not reported; and SGLT2i, sodium glucose cotransporter 2 inhibitor.

https://www.jacc.org/doi/10.1016/j.jacc.2021.12.012

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TABLE 15 Benefits of Evidence-Based Therapies for Patients With HFrEF (3-6,8,10-14,23,31-42)

Evidence-Based Therapy	Relative Risk Reduction in All-Cause Mortality in Pivotal RCTs, %	NNT to Prevent All-Cause Mortality Over Time*	NNT for All-Cause Mortality (Standardized to 12 mo)	NNT for All- Cause Mortality (Standardized to 36 mo)
ACEi or ARB	17	22 over 42 mo	77	26
ARNi†	16	36 over 27 mo	80	27
Beta blocker	34	28 over 12 mo	28	9
Mineralocorticoid receptor antagonist	30	9 over 24 mo	18	6
SGLT2i	17	43 over 18 mo	63	22
Hydralazine or nitrate‡	43	25 over 10 mo	21	7
CRT	36	12 over 24 mo	24	8
ICD	23	14 over 60 mo	70	23

*Median duration follow-up in the respective clinical trial.
†Benefit of ARNi therapy incremental to that achieved with ACEi therapy. For the other medications shown, the benefits are based on comparisons to placebo control.
‡Benefit of hydralazine-nitrate therapy was limited to African American patients in this trial.

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; CRT, cardiac resynchronization therapy; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; NNT, number needed to treat; RCT, randomized controlled trial; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

https://www.jacc.org/doi/10.1016/j.jacc.2021.12.012

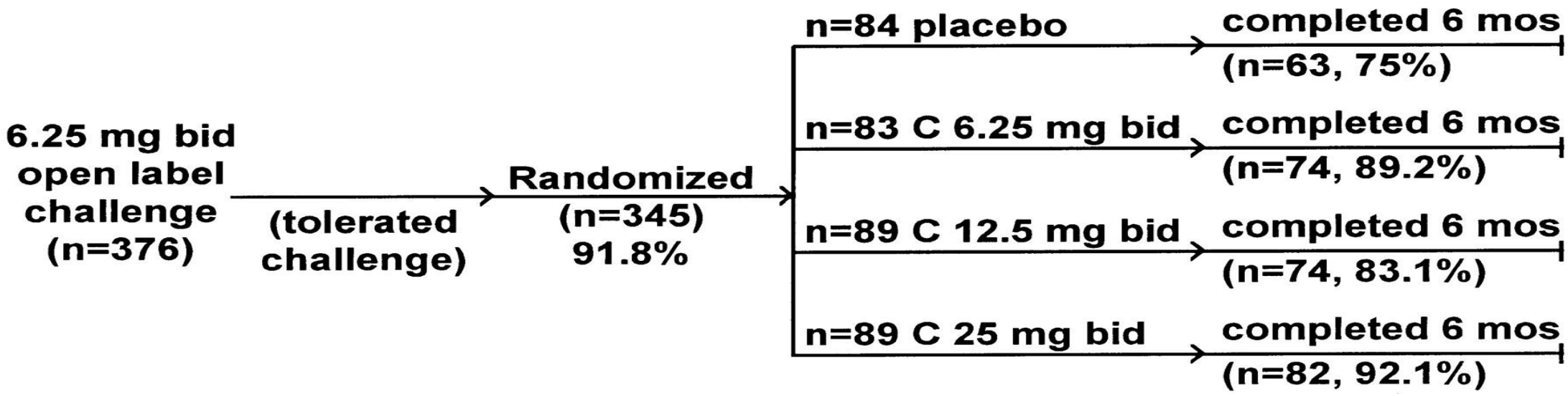
How many patients with HFrEF are receiving Guideline Directed Medical Therapy?

- **The CHAMP-HF (Change the Management of Patients with Heart Failure) registry** included outpatients in the United States with chronic HFrEF receiving at least 1 oral medication for management of HF.
- **3,518 patients from 150 primary care and cardiology practices were incl**uded. Mean age was 66 +/- 13 years, 29% were female, and mean EF was 29 +/- 8%.
- Among eligible patients, **27%, 33%, and 67% were not prescribed ACEI/ARB/ARNI, beta-blocker, and MRA therapy, respectively.**
- **When medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%), whereas most patients were receiving target doses of MRA therapy (77%).**
- **Among patients eligible for all classes of medication, 1% were simultaneously receiving target doses of ACE/ARB/ARNI, beta-blocker, and MRA.**
  - (J Am Coll Cardiol 2018;72:351–66)

Cost Barriers

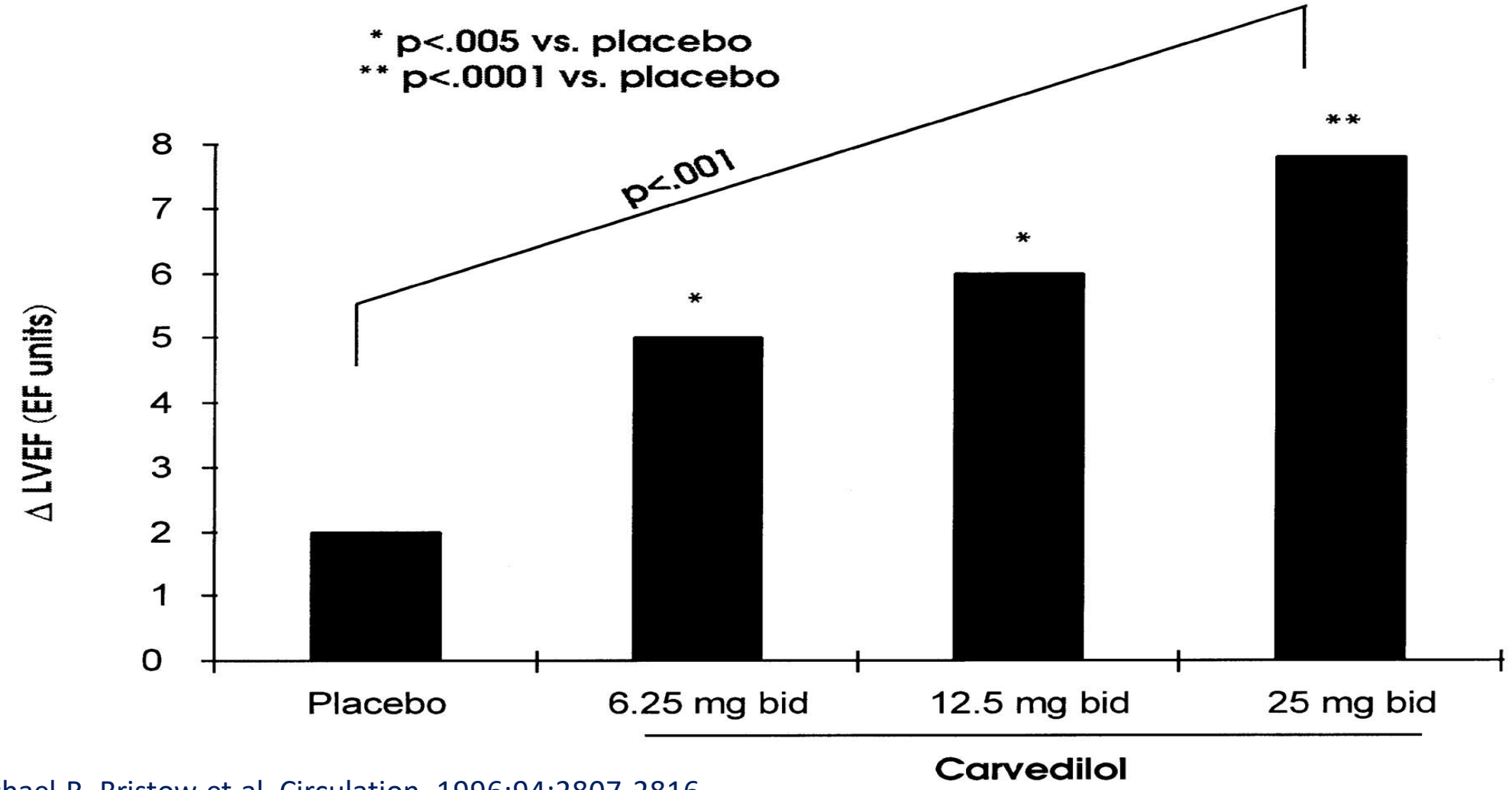
- The current study involved **all 4068 Medicare prescription drug plans implemented in 2020.** Study authors analyzed cost sharing, prior authorization, and step therapy. Here are the key findings:
  - **Tier ≥3 cost sharing was required by 99.1% of plans for ARNI and 98.5% for at least 1 SGLT2 inhibitor.**
  - Only ARNI required prior authorization (24.3% of plans), and step therapy was required only for SGLT2 inhibitors (5.4%) and eplerenone (0.8%).
  - The **median 30-day standard coverage out-of-pocket cost of quadruple therapy was $94 (IQR: $84-$100), including $47 (IQR: $40-$47) for ARNI and $45 (IQR: $40-$47) for SGLT2 inhibitors.**
  - **The median annual out-of-pocket cost of quadruple therapy was $2217** (IQR: $1956-$2579) compared with $1319 (IQR: $1067-$1675) when excluding SGLT2 inhibitors, and $1322 (IQR: $1025-$1588) when including SGLT2 inhibitors and substituting an ACE inhibitor or angiotensin receptor blocker for ARNI therapy.
  - **The median 30-day out-of-pocket cost of generic regimens was $3** (IQR: $0-$9).

Study design and overall outcome of the MOCHA trial
(dose response of carvedilol in chronic heart failure, protocol 220).



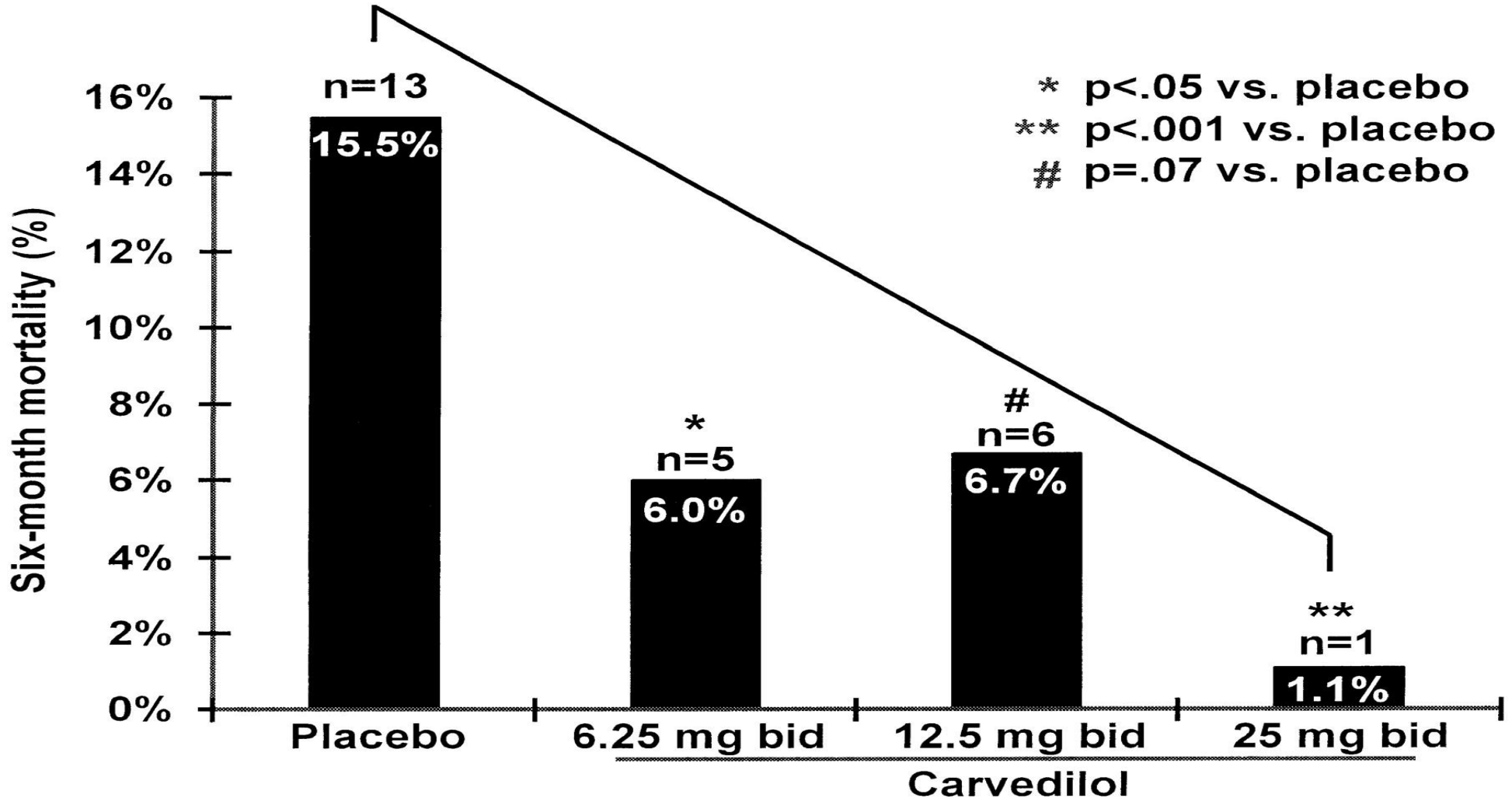
Michael R. Bristow et al. Circulation. 1996;94:2807-2816

Carvedilol protocol 220 (MOCHA): LVEF data at end of 6-month maintenance period as change (Δ) from baseline values.



Michael R. Bristow et al. Circulation. 1996;94:2807-2816

Carvedilol protocol 220 (MOCHA): six-month crude mortality as deaths per randomized patients×100.



Michael R. Bristow et al. Circulation. 1996;94:2807-2816

Beta-blockers in Patients with COPD/Asthma?

- **Bisoprolol** has data for use in heart failure and coronary artery disease and **has a beta-1/2 receptor selectivity ratio of 14:1, which is higher than either atenolol (5:1) or metoprolol (2:1)** [Br J Pharmacol 2005; 144: 317–322].
- **In a cross-over study of 51 patients with COPD and heart failure, directly comparing 6 weeks of bisoprolol, metoprolol and carvedilol** [J Am Coll Cardiol 2010; 55: 1780–1787], **FEV1 was lowest with carvedilol and highest with bisoprolol with metoprolol in between.**

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Recommendation for HF With Improved Ejection Fraction
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	RECOMMENDATION
1	B-R	1. In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic (1).

In an **open-label RCT, phased withdrawal of HF medications in patients with previous dilated cardiomyopathy** (DCM)—**who were now asymptomatic, whose LVEF had improved from <40% to ≥50%,** whose left ventricular end-diastolic volume (LVEDV) had normalized, and who had an NT-proBNP concentration <250 ng/L—**resulted in relapse of cardiomyopathy and HF in 40% of the patients within 6 months.** Relapse was defined by at least 1 of these: 1) a reduction in LVEF by >10% and <50%; 2) an increase in LVEDV by >10% and to higher than the normal range; 3) a 2-fold rise in NT-proBNP concentration and to >400 ng/L; or 4) clinical evidence of HF. **Treatment was withdrawn successfully in only 50% of patients**. Secondary analyses showed worsening Kansas City Cardiomyopathy Questionnaire scores, a substantial reduction in LVEF, and nonsignificant increases in NT-proBNP and LV volumes with withdrawal of HF medications. **Lancet 2019;393:61-73**

https://www.jacc.org/doi/10.1016/j.jacc.2021.12.012

New Recommendations in HFmrEF (LVEF 41-49%)

SGLT2i

- Can be beneficial in decreasing HHF and CV mortality

2a | B-R

ARNi, ACEi, or ARB; MRA; BB

- May be considered to reduce risk of HHF and CV mortality, particularly among patients with LVEF on lower end of this spectrum

2b | B-NR

CV, cardiovascular; HHF, hospitalization for HF

Circulation. 2022;145:00–00. DOI: 10.1161/CIR.0000000000001063

New Recommendations in HFpEF (LVEF ≥50%)

SGLT2i	MRA	ARNi
• Can be beneficial in decreasing HHF and CV mortality	• May be considered in selected patients to decrease HHF, particularly among patients with LVEF on lower end of this spectrum	• May be considered in selected patients to decrease HHF, particularly among patients with LVEF on lower end of this spectrum
2a B-R	2b B-R	2b B-R

CV, cardiovascular; HHF, hospitalization for HF

Circulation. 2022;145:00–00. DOI: 10.1161/CIR.0000000000001063

Joint ADA/EASD—Management of Hyperglycaemia in Type 2 Diabetes

Friday, September 23, 2022

12:15 – 13:45 CEST

Co-Chair: John B. Buse, MD, PhD

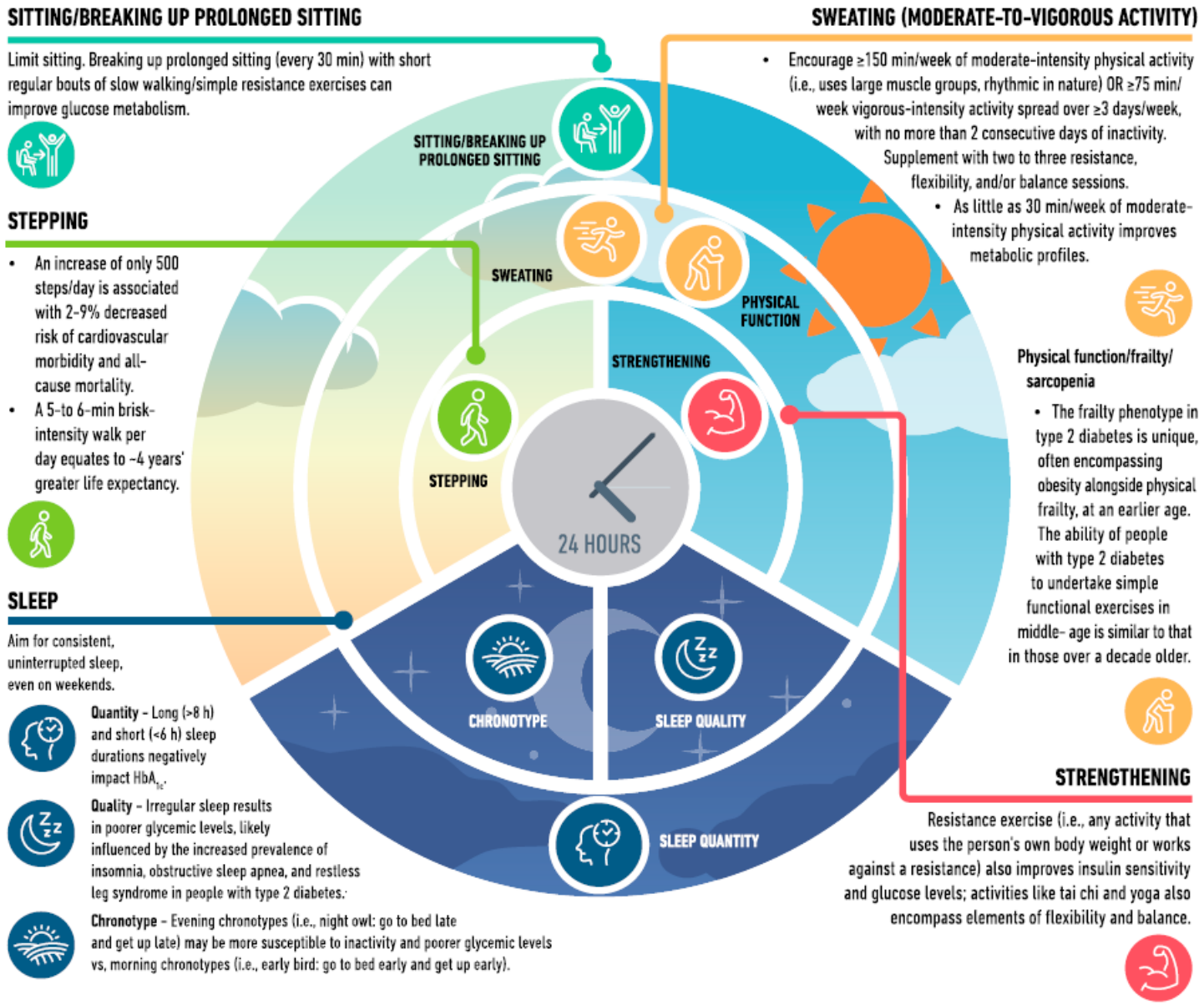
Co-Chair: Melanie J. Davies, MB ChB, MD

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB *Diabetes Care* 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

American Diabetes Association.

EASD European Association for the Study of Diabetes

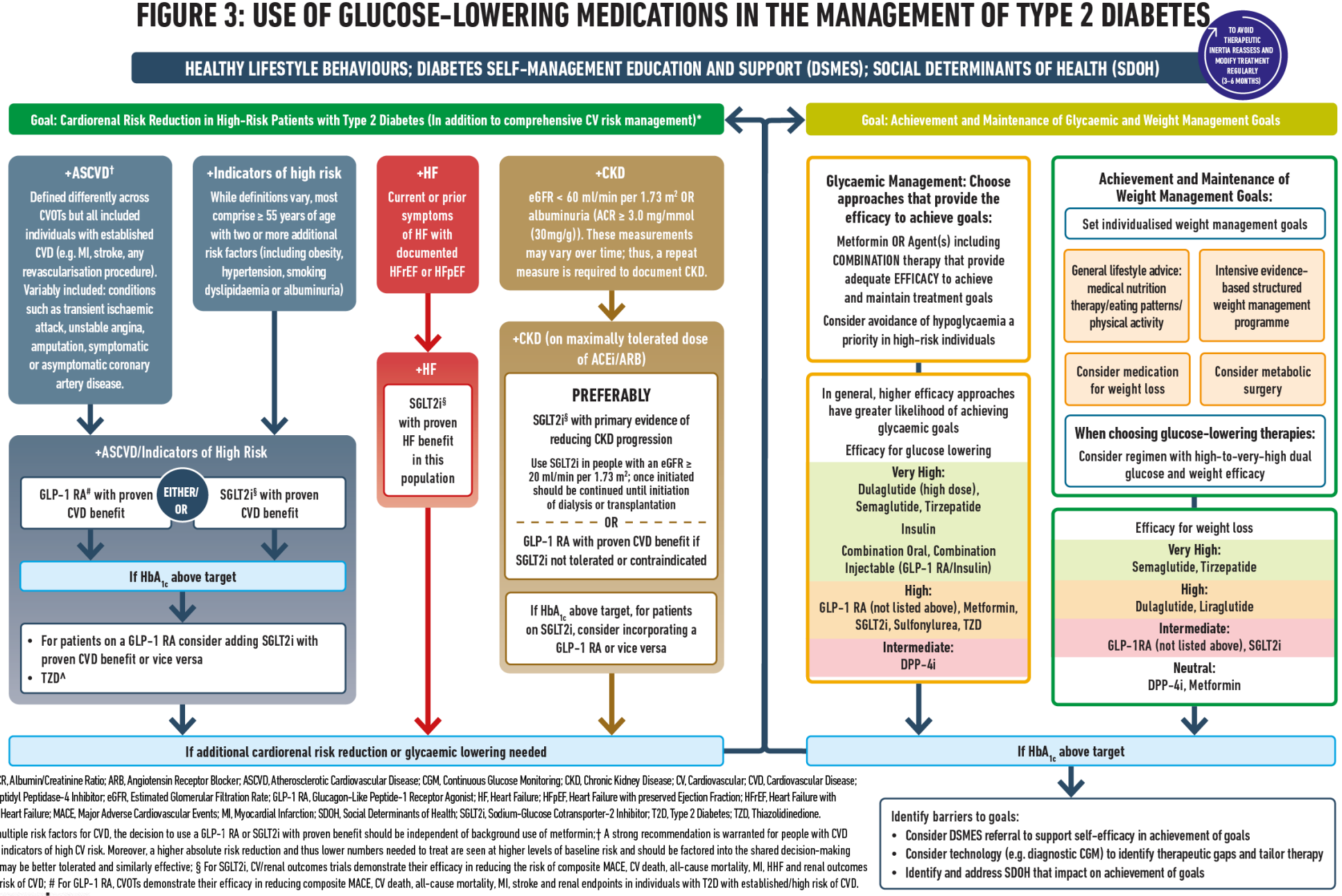
IMPORTANCE OF 24-HOUR PHYSICAL BEHAVIORS FOR TYPE 2 DIABETES



American Diabetes Association.

EASD European Association for the Study of Diabetes

FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

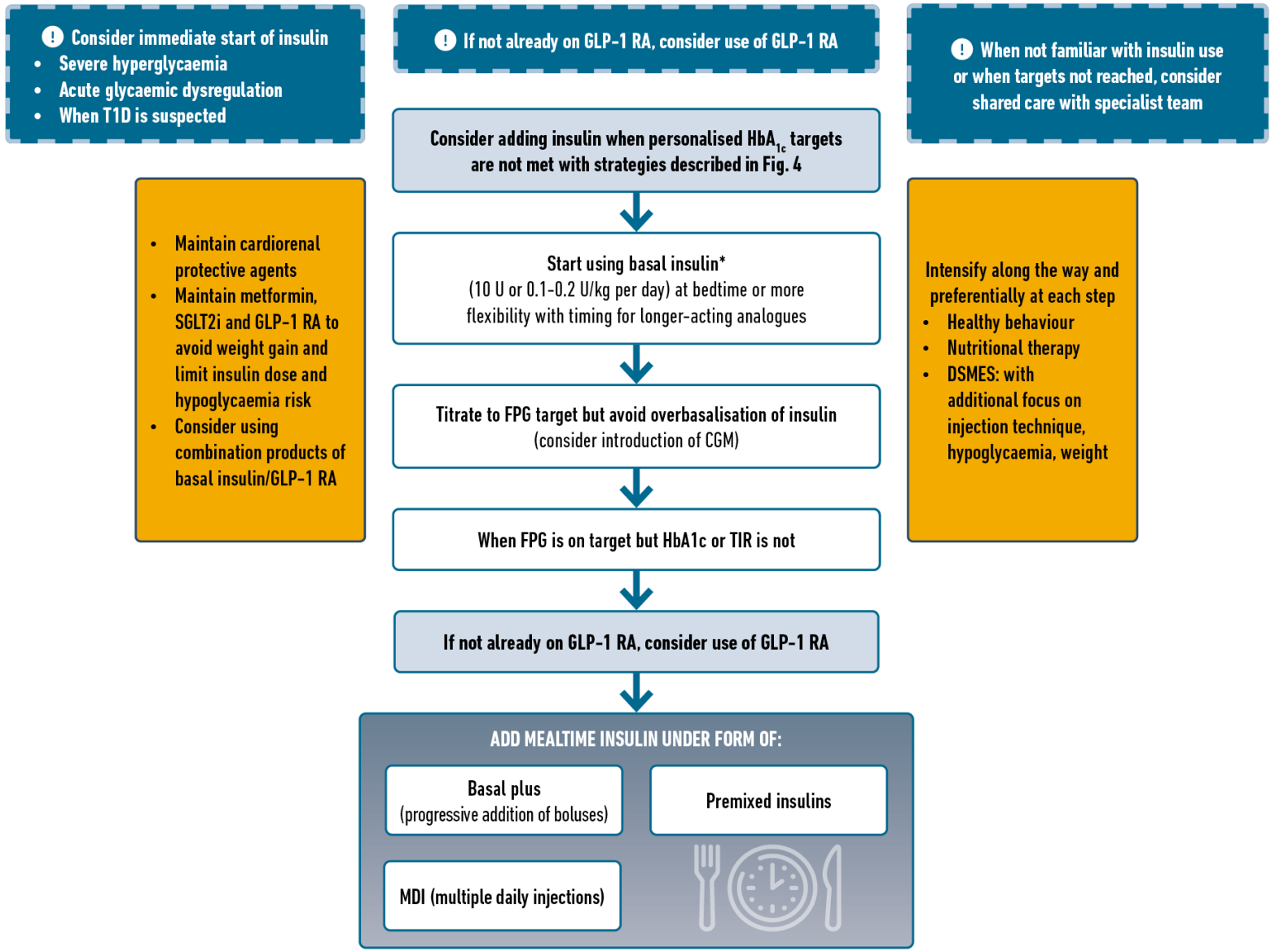
American Diabetes Association.

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

EASD European Association for the Study of Diabetes

FIGURE 5: PLACE OF INSULIN[1]



*NPH Insulin or preferably analogue to reduce nocturnal hypoglycaemia risk

CGM, Continuous Glucose Monitoring; DSMES, Diabetes Self-Management Education and Support; FPG, Fasting Plasma Glucose; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T1D, Type 1 Diabetes; TIR, Time in Range.

1, More details can be found in Davies M, D'Alessio DA, Fradkin J et al. Management of Hyperglycaemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018 61(12):2461–2498, and American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S125–43.

American Diabetes Association.

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

EASD European Association for the Study of Diabetes

Higher Dose Dulaglutide AWARD 11 Trial

Treatment	A1C Reduction *(baseline 8.6 percent)*	Weight Reduction *[baseline 211.4 lbs. (95.9 kg)]*
dulaglutide 4.5 mg	-1.9 percent*	-10.4 lbs. (-4.7 kg)*
dulaglutide 3 mg	-1.7 percent*	-8.8 lbs. (-4.0 kg)*
Trulicity 1.5 mg	-1.5 percent	-6.8 lbs. (-3.1 kg)

*Denotes statistical significance compared to Trulicity 1.5 mg

The safety and tolerability profile of the investigational dulaglutide doses (3 mg and 4.5 mg) was consistent with the known profile of Trulicity 1.5 mg. The most commonly reported adverse events across each of the doses were gastrointestinal-related.

Results at 52-weeks were consistent with the 36-week results and further details will be disclosed at a later date. The AWARD-11 results have been submitted to regulatory authorities in the U.S. and Europe for review.

Lilly Press Release May 8, 2020 also published in the Journal of the Endocrine Society

Sept. 3, 2020 /PRNewswire/ -- The U.S. Food and Drug Administration (FDA) today approved two additional doses of Eli Lilly and Company's (NYSE: LLY) Trulicity® (dulaglutide). The approval expands the label of once-weekly Trulicity to include 3.0 mg and 4.5 mg doses based on data from AWARD-11.

Semaglutide - Ozempic New Dose

- **28 March 2022 – the US Food and Drug Administration (FDA) has approved a 2.0 mg dose of Ozempic® (once-weekly semaglutide subcutaneous injection), a glucagon-like peptide-1 (GLP-1) analogue for the treatment of adults with type 2 diabetes.** Ozempic® is now approved in the US at 0.5 mg,1.0 mg and 2.0 mg doses for the treatment of type 2 diabetes in adults. Further, Ozempic® is indicated to reduce the risk of major cardiovascular events such as heart attack, stroke or death in adults with type 2 diabetes and known heart disease.
- The FDA approval is based on the results from the **SUSTAIN FORTE trial.** In the trial, people treated with semaglutide 2.0 mg achieved a statistically significant and superior reduction in HbA1c at week 40 compared to semaglutide 1.0 mg. In the trial, both doses of semaglutide appeared to have a safe and well-tolerated profile. The most common adverse events were gastrointestinal. Compared to semaglutide 1.0 mg, the gastrointestinal adverse events were similar for semaglutide 2.0 mg.

Semaglutide – Sustain Forte Trial

- **SUSTAIN FORTE trial, a phase 3b 40-week, efficacy and safety trial with once-weekly semaglutide 2.0 mg vs once-weekly semaglutide 1.0 mg as add-on to metformin and/or sulfonylureas in 961 people with type 2 diabetes in need for treatment intensification.** The trial achieved its **primary endpoint by demonstrating a statistically significant and superior reduction in HbA1c at week 40** with semaglutide 2.0 mg compared to semaglutide 1.0 mg.

	Trial product estimand[1]		**Treatment policy estimand[2]**	
Once-weekly semaglutide	2.0 mg	1.0 mg	2.0 mg	1.0 mg
HbA_{1c} reduction	2.2%*	1.9%	2.1%*	1.9%
Body weight reduction	6.9 kg*	6.0 kg	6.4 kg	5.6 kg

*Statistically significant vs once-weekly semaglutide 1.0 mg

1 Based on the trial product estimand: treatment effect if all people adhered to treatment and did not initiate other type 2 diabetes therapies
2 Based on the treatment policy estimand: treatment effect regardless of treatment adherence or initiation of other type 2 diabetes therapies

Tirzepatide – Mounjaro by Lilly

- **May 13, 2022, the U.S. Food and Drug Administration approved Mounjaro (tirzepatide) injection, a first-in-class medicine that activates both the GLP-1 and GIP receptors**, which leads to improved blood sugar control. Tirzepatide is **administered by sub-Q injection skin once weekly**, with the dose adjusted as tolerated to meet blood sugar goals. It is indicated to improve blood sugar control in adults with type 2 diabetes, as an addition to diet and exercise. Tirzepatide was effective at improving blood sugar and was more effective than the other diabetes therapies with which it was compared in clinical studies.
- **Three different doses of terzepatide (5 milligrams, 10 milligrams and 15 milligrams) were evaluated in five clinical trials as either a stand-alone therapy or as an add-on to other diabetes medicines.** The efficacy of Mounjaro was **compared to placebo, a GLP-1 receptor agonist (semaglutide) and two long-acting insulin analogs.**
  - https://www.fda.gov/news-events/press-announcements/fda-approves-novel-dual-targeted-treatment-type-2-diabetes

Tirzepatide – Mounjaro

- **Tirzepatide enhances first- and second-phase insulin secretion, and reduces glucagon levels, both in a glucose dependent manner.**
  - **Tirzepatide reduces fasting and postprandial glucagon concentrations. Tirzepatide 15 mg reduced fasting glucagon concentration by 28% and glucagon AUC after a mixed meal by 43%, compared with no change for placebo after 28 weeks of treatment.**
  - **Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time.**
  - **Tirzepatide slows post-meal glucose absorption, reducing postprandial glucose.**
  - **Elimination half-life of approximately 5 days**

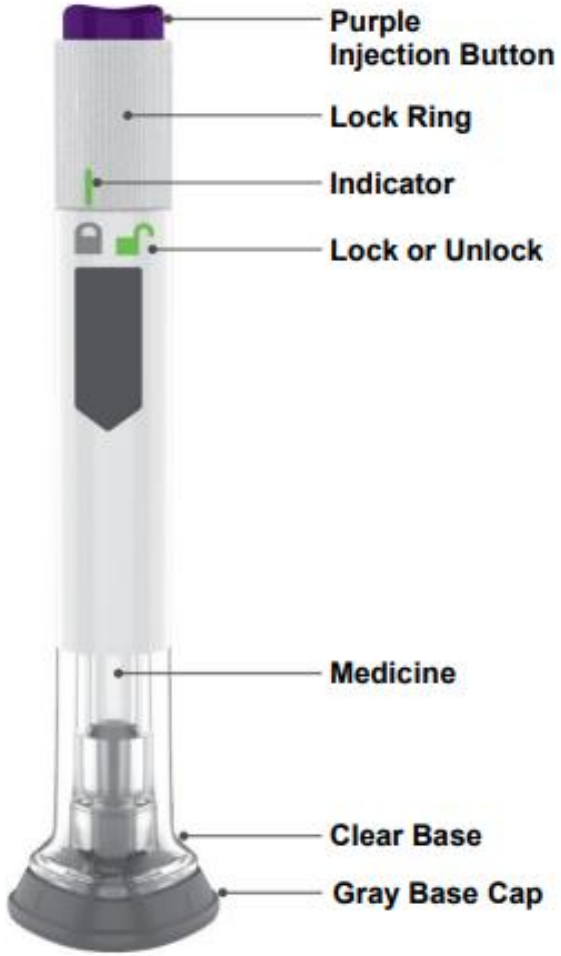
Table 4: Results at Week 40 in a Trial of MOUNJARO versus Semaglutide 1 mg in Adult Patients with Type 2 Diabetes Mellitus Added to Metformin

SURPASS 2 Trial	Semaglutide 1 mg	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	468	470	469	469
HbA1c (%)				
Baseline (mean)	8.3	8.3	8.3	8.3
Change at Week 40[b]	-1.9	-2.0	-2.2	-2.3
Difference from semaglutide[b] (95% CI)	--	-0.2[c] (-0.3, -0.0)	-0.4[d] (-0.5, -0.3)	-0.5[d] (-0.6, -0.3)
Patients (%) achieving HbA1c <7%[e]	79	82	86[f]	86[f]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	171	174	174	172
Change at Week 40[b]	-49	-55	-59	-60
Body Weight (kg)				
Baseline (mean)	93.7	92.5	94.8	93.8
Change at Week 40[b]	-5.7	-7.6	-9.3	-11.2
Difference from semaglutide[b] (95% CI)	--	-1.9[c] (-2.8, -1.0)	-3.6[d] (-4.5, -2.7)	-5.5[d] (-6.4, -4.6)

Tirzepatide – Mounjaro

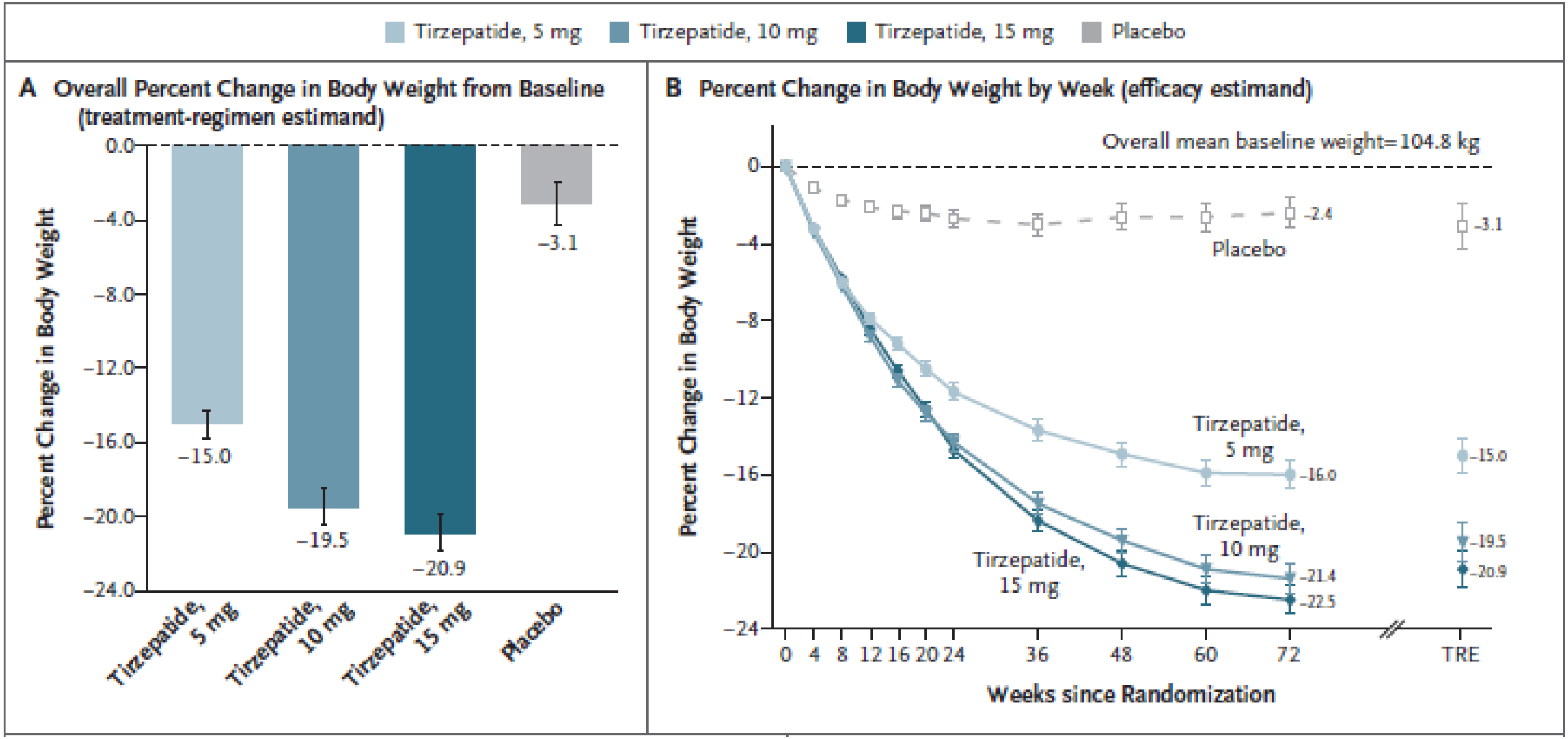
Available in **boxes of 4 single dose pens**

- 2.5 mg/0.5 mL single-dose pen
- 5 mg/0.5 mL single-dose pen
- 7.5 mg/0.5 mL single-dose pen
- 10 mg/0.5 mL single-dose pen
- 12.5 mg/0.5 mL single-dose pen
- 15 mg/0.5 mL single-dose pen
- **Cost: list price of $974.33 for four weekly doses regardless of dose size, a cost that adds up to about $12,666 per year**
- Store your Pen in the refrigerator between 36°F to 46°F (2°C to 8°C). Do not freeze!
- You may store your Pen at room temperature up to 86°F (30°C) for up to 21 days and protect from light.



SURMOUNT-1 Trial : Tirzepatide Once Weekly for the Treatment of Obesity

- A phase 3 double-blind, randomized, controlled trial, in **2539 adults with a body-mass index (BMI of 30 or more, or 27 or more and at least one weight-related complication, excluding diabetes**, in a 1:1:1:1 ratio to receive once-weekly, subcutaneous **tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 72 weeks, including a 20-week dose-escalation period.**
- **Coprimary end points were the percentage change in weight from baseline and a weight reduction of 5% or more.**
  - June 4, 2022, at NEJM.org. DOI: 10.1056/NEJMoa2206038



– June 4, 2022, at NEJM.org. DOI: 10.1056/NEJMoa2206038

Section 11.

Chronic Kidney Disease and Risk Management

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Connected for Life

Chronic Kidney Disease—Treatment

11.2 Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease. A

11.3a For **patients with type 2 diabetes and diabetic kidney disease, consider use of a sodium–glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥25 mL/min/1.73 m^2 and urinary albumin ≥300 mg/g creatinine is recommended to reduce chronic kidney disease progression and cardiovascular events. A**

11.3b In patients with type 2 diabetes and chronic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors additionally for cardiovascular risk reduction when estimated glomerular filtration rate and urinary albumin creatinine are ≥25 mL/min/1.73 m2 or >300 mg/g, respectively (Fig. 9.3).

A

Chronic Kidney Disease—Treatment (continued)

11.3c In **patients with chronic kidney disease who are at increased risk for cardiovascular events or chronic kidney disease progression or are unable to use a sodium–glucose cotransporter 2 inhibitor, a nonsteroidal mineralocorticoid receptor antagonist (finerenone) is recommended to reduce chronic kidney disease progression and cardiovascular events** (Table 9.2).A

11.3d In patients with chronic kidney disease who have ≥300 mg/g urinary albumin, a reduction of 30% or greater in mg/g urinary albumin is recommended to slow chronic kidney disease progression. B

11.4 Optimization of blood pressure control and reduction in blood pressure variability to reduce the risk or slow the progression of chronic kidney disease is recommended. A

Chronic Kidney Disease—Treatment (continued)

11.5 **Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (<30%) in the absence of volume depletion. A**

11.6 For people with nondialysis dependent stage 3 or higher chronic kidney disease, dietary protein intake should be a maximum of 0.8 g/kg body weight per day (the recommended daily allowance). A For patients on dialysis, higher levels of dietary protein intake should be considered, since malnutrition is a major problem in some dialysis patients. B

Chronic Kidney Disease—Treatment (continued)

11.7 **In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) B and is strongly recommended for those with urinary albumin-to creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m2. A**

11.8 Periodically monitor serum creatinine and potassium levels for the development of increased creatinine or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. B

Chronic Kidney Disease—Treatment (continued)

11.9 **An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of chronic kidney disease in patients with diabetes who have normal blood pressure, normal urinary albumin-to-creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. A**

11.10 Patients should be referred for evaluation by a nephrologist if they have an estimated glomerular filtration rate <30 mL/min/1.73 m2. A

11.11 Promptly refer to a nephrologist for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. A

Finerenone – Kerendia by Bayer

- **July 9, 2021 FDA Priority Review Approval - Finerenone a non-steroidal mineralocorticoid receptor antagonist (MRA) indicated to reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes.**

Finerenone – Kerendia

- **DRUG INTERACTIONS: Finerenone is a CYP3A4 substrate; coadministration with a strong CYP3A4 inhibitor (itraconazole) increased finerenone exposure by more than 400%.** Concomitant use of **finerenone with strong CYP3A4 inhibitors is contraindicated, and concomitant intake of grapefruit or grapefruit juice is not recommended.**
- **Coadministration with a moderate CYP3A4 inhibitor (erythromycin) increased finerenone mean AUC and Cmax by 248% and 88%, respectively, while coadministration with a weak CYP3A4 inhibitor (amiodarone) increased finerenone AUC by 21%.** Concomitant use of finerenone with a moderate or weak CYP3A4 inhibitor **may increase the risk of adverse reactions.** If concomitant use is necessary**, monitor serum potassium during therapy initiation or dosage adjustment** of either finerenone or the moderate or weak CYP3A4 inhibitor, and adjust finerenone dosage as appropriate.

Finerenone – Kerendia

DOSING: The recommended starting finerenone dose is based on baseline eGFR; see Table 3 for a summary of recommended starting doses. The target daily dose is 20 mg. (Kerendia 2021)

Table 3. Recommended Starting Dose of Finerenone Based on eGFR (Kerendia July 2021)	
Baseline eGFR	**Starting finerenone dose**
≥60 mL/minute/1.73 m^2	20 mg once daily
25 to <60 mL/minute/1.73 m^2	10 mg once daily
<25 mL/minute/1.73 m^2	Not recommended

Finerenone can be taken without regard to food. The tablets may be crushed and mixed with water or soft foods immediately prior to oral administration. If a dose is missed, it should be taken as soon as possible,

Table 4. Recommended Finerenone Dose Adjustments Based on Serum Potassium and Current Finerenone Dose (Kerendia July 2021)		
Serum potassium (mEq/L)	**Current finerenone dose**	
	10 mg once daily	**20 mg once daily**
≤4.8 mEq/L	Increase dose to 20 mg once daily.[a]	Maintain 20 mg once daily.
>4.8 to 5.5 mEq/L	Maintain 10 mg once daily.	Maintain 20 mg once daily.
>5.5 mEq/L	Withhold finerenone. Consider restarting at 10 mg once daily when serum potassium ≤5 mEq/L.	Withhold finerenone. Restart at 10 mg once daily when serum potassium ≤5 mEq/L.
[a] If eGFR has decreased >30% from previous measurement, maintain 10 mg dose.		

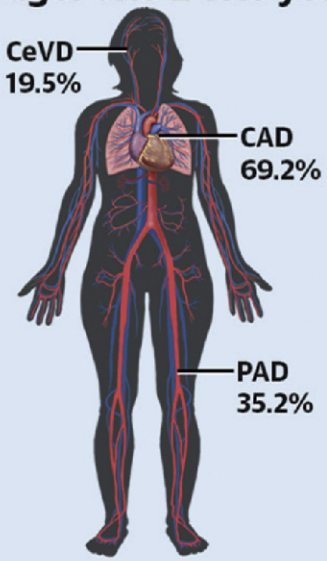
Finerenone – Kerendia

- **Tablets: 10 mg and 20 mg once a day with or without food.**
- **Cost for both strengths is ~ $600.00 for 30 tablets**
- **Should we now consider triple therapy for our patients with diabetes and CKD? (ACEI or ARB plus an SGLT-2 inhibitor and now finereone)**
  - **We have good data with an ACEI or ARB plus an SGLT-2 inhibitor and also with an ACEI or ARB plus finereone but only very limited data with all three. (4.6% of pts in FIDELIO-DKD trial were also taking an SGLT-2 inhibitor and they did appear to have a lower risk of hyperkalemia? We need more data!**

CENTRAL ILLUSTRATION: Statin Use in 601,934 Patients With Atherosclerotic Cardiovascular Disease on January 31, 2019

Study Population

601,934 patients with ASCVD
Mean age: 67.5 ± 13.3 years



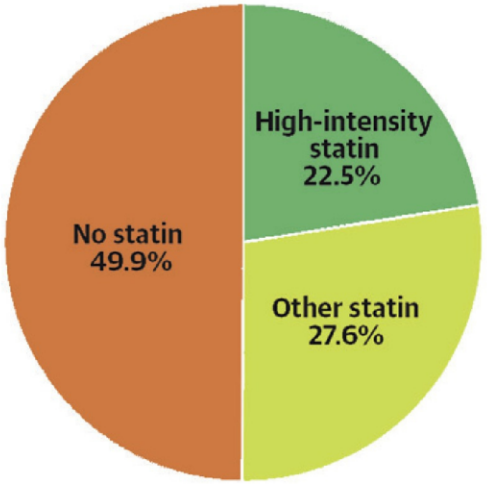
Outcomes

Statin usage on January 31, 2019 ± 30 days

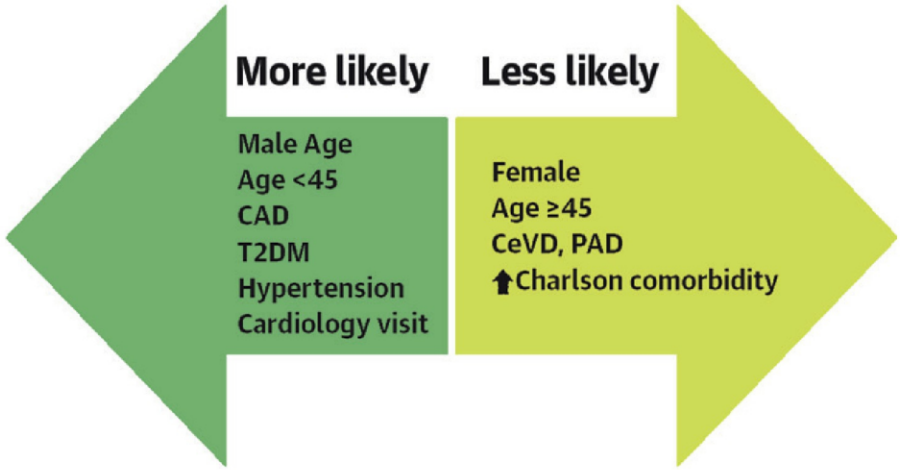
Proportion of days covered

Results

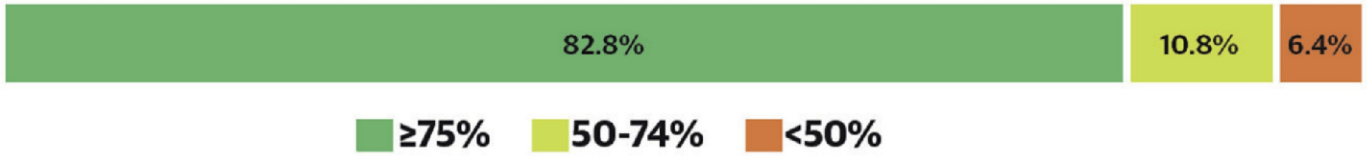
Proportion on high-intensity statin vs other statin vs no statin



Odds of high (vs other) intensity statin use



Proportion of days covered



Nelson AJ, et al. J Am Coll Cardiol. 2022;79(18):1802-1813.

Inclisiran – Leqvio by Novartis

- **Dec 22, 2021, the FDA approved Inclisiran-Leqvio** a small interfering RNA directed to PCSK9 (proprotein convertase subtilisin kexin type 9) mRNA indicated **as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).**
- **Limitations of Use: The effect of inclisiran on cardiovascular morbidity and mortality has not been determined but is being studied in the ongoing ORION 4 Trial in ~15,000 patients with ASCVD an on max tolerated statin dose.**
  (https://www.clinicaltrials.gov/ct2/show/NCT03705234?term=ORION+4&draw=2&rank=1)

Inclisiran – Leqvio

Table 3: Changes in Lipid Parameters in Patients with ASCVD on Maximally Tolerated Statin Therapy (Mean % Change from Baseline to Day 510 in Study 2)

Treatment Group	LDL-C	Total Cholesterol	Non-HDL-C	ApoB
Day 510 (mean percentage change from baseline)				
Placebo (n = 702)	4	2	2	1
LEQVIO (n = 712)	-46	-28	-42	-39
Difference from placebo (LS Mean) (95% CI)	-51 (-54, -47)	-30 (-32, -28)	-44 (-47, -41)	-40 (-42, -37)

ApoB = apolipoprotein B; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

ORION-11, (NCT03400800) was a multicenter, double-blind, randomized, placebo-controlled 18month trial in which 1414 adults with ASCVD were randomized 1:1 to receive subcutaneous injections of either LEQVIO 284 mg (n = 712) or placebo (n = 702)

- Change in **median triglyceride level at day 510: −12%** in the inclisiran group and −5% in the placebo group; treatment difference was −7%.
- Change in **median lipoprotein(a) at day 540: −18.6%** in the inclisiran group, with no change in the placebo group; treatment difference was −18.6%.
- Change in **HDL-C at day 510: +10.2%** in the inclisiran group and +4.1% in the placebo group; treatment difference was +6.1%.
- Change in median hsCRP at day 540 (safety population): **Median hsCRP was unchanged** in the inclisiran group and was −8.9% in the placebo group; treatment difference was +8.9%.

Inclisiran – Leqvio

- **DOSING:** Inclisiran is for administration via **subcutaneous injection** by a health care provider **during the initial visit, at 3 months, then every 6 months thereafter.** In clinical trials, the **inclisiran sodium dose used was 300 mg (which corresponds to an inclisiran free acid dose of 284 mg).** Patient should remain in the clinic for observation for at least 30 minutes after the injection.
- Injection: 284 mg/1.5 mL (189 mg/mL) of inclisiran as a clear, and colorless to pale yellow solution in a single-dose prefilled syringe.
- **Cost: ~$3,250.00/dose or $6,500.00/year**

Store at controlled room temperature