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 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.
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>
<thead>
<tr>
<th>Medical indication group</th>
<th>Specific underlying medical condition</th>
<th>19–64 Age group, yrs</th>
<th>≥65 Age group, yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥1 years later*</td>
</tr>
<tr>
<td>Underlying medical conditions or other risk factors</td>
<td>Alcoholism</td>
<td>1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥1 years later$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic heart disease†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic lung disease§</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
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<td></td>
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<tr>
<td></td>
<td>Cochlear implant</td>
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<tr>
<td></td>
<td>CSF leak</td>
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<td></td>
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<tr>
<td></td>
<td>Congenital or acquired asplenia</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Sickle cell disease or other hemoglobinopathies</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Chronic renal failure**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Congenital or acquired immunodeficiencies**,**††</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Generalized malignancy**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV infection**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hodgkin disease**</td>
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<td></td>
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<tr>
<td></td>
<td>Iatrogenic immunosuppression**,**§§</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Leukemia**</td>
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<td></td>
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<tr>
<td></td>
<td>Lymphoma**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solid organ transplant**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
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.
COVID-19 Vaccination Schedule for Most People
(People who are NOT Moderately or Severely Immunocompromised)

**People ages 6 months through 4 years**
- Moderna: Primary → Primary (In 4-8 weeks)
- Pfizer-BioNTech: Primary → Primary (In 3-8 weeks)
  - OR -
  - Moderna: Primary → Primary (In 4-8 weeks)
  - Pfizer-BioNTech: Primary → Primary (In at least 8 weeks)

**People ages 5 through 11 years**
- Moderna: Primary → Primary (In 4-8 weeks)
- Pfizer-BioNTech: Primary → Primary (In 3-8 weeks)
  - OR -
  - Moderna: Primary → Monovalent Booster (In at least 5 months)
  - Pfizer-BioNTech: Primary → Primary (In at least 8 weeks)

**People ages 12 years and older**
- Moderna, Novavax, or Pfizer-BioNTech:
  - Primary → Primary (In 3-8 weeks (Novavax, Pfizer) or in 4-8 weeks (Moderna))
  - Primary → Bivalent booster* (In at least 2 months)

**People ages 18 years and older who previously received Janssen primary series dose†**
- Primary → Bivalent booster* (In at least 2 months)

*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-a.html#appendix-a

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.
At-a-Glance
COVID-19 Vaccination Schedule for People Who Are Moderately or Severely Immunocompromised

People ages 6 months through 4 years

**Moderna**
- In 4 weeks
- In at least 4 weeks
- **Primary**
- **Primary**
- **Primary**

- OR -

**Pfizer-BioNTech**
- In 3 weeks
- In at least 8 weeks
- **Primary**
- **Primary**
- **Primary**

People ages 5 years through 11 years

**Moderna**
- In 4 weeks
- In at least 4 weeks
- **Primary**
- **Primary**
- **Primary**

- OR -

**Pfizer-BioNTech**
- In 3 weeks
- In at least 4 weeks
- **Primary**
- **Primary**
- **Primary**
- In at least 3 months
- **Monovalent 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
COVID-19 Vaccination Schedule for People Who Are Moderately or Severely Immunocompromised

People ages 12 years and older

Modern or Pfizer-BioNTech

- In 3-8 weeks (Pfizer) or in 4 weeks (Moderna)
  → Primary

- In at least 4 weeks
  → Primary

- In at least 2 months
  → Primary

- Bivalent booster

- OR -

Novavax

- In 3 weeks
  → Primary

- In at least 2 months
  → Primary

- Bivalent booster

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

- In at least 4 weeks
  → Primary

- Add mRNA dose

- In at least 2 months
  → Bivalent booster

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

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

- Any dose (primary or booster)
  → In at least 2 weeks

- EVUSHED™ dose every 6 months

- No minimum interval from EVUSHED™ to COVID-19 vaccine

- Any subsequent COVID-19 vaccine dose

- At least 2 weeks from COVID-19 vaccine to EVUSHED™

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.

† Janssen COVID-19 Vaccine should only be used in certain limited situations. See: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-usa-appendix.html#appendix-g
Global Initiative for Asthma (GINA)
What’s new in GINA 2022?

GINA Global Strategy for Asthma Management and Prevention

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Adults & adolescents
12+ years

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

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

NOTE ICS-formoterol is NOT FDA Approved for this indication

Other controller options for either track (limited indications, or less evidence for efficacy or safety)

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

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

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

STEPS 1–2
As-needed low dose ICS-formoterol

STEP 1
Take ICS whenever SABA taken

STEP 2
Low dose maintenance ICS

STEP 3
Low dose maintenance ICS-LABA

STEP 4
Medium dose maintenance ICS-formoterol

STEP 4
Medium/high dose maintenance ICS-LABA

STEP 5
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP

STEP 5
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 low-dose ICS-formoterol

RELIEVER: As-needed short-acting beta-2-agonist

GINA 2022, Box 3-5A
© Global Initiative for Asthma, www.ginasthma.org
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
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)
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.
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 FEV₁ and symptoms (Evidence A).

Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV₁ 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 FEV₁ 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):

<table>
<thead>
<tr>
<th>STRONG SUPPORT</th>
<th>CONSIDER USE</th>
<th>AGAINST USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• History of hospitalization(s) for exacerbations of COPD#</td>
<td>• 1 moderate exacerbation of COPD per year#</td>
<td>• Repeated pneumonia events</td>
</tr>
<tr>
<td>• ≥ 2 moderate exacerbations of COPD per year#</td>
<td>• Blood eosinophils ≥ 100 to &lt; 300 cells/μL</td>
<td>• Blood eosinophils &lt;100 cells/μL</td>
</tr>
<tr>
<td>• Blood eosinophils ≥ 300 cells/μL</td>
<td></td>
<td>• History of mycobacterial infection</td>
</tr>
<tr>
<td>• History of, or concomitant, asthma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#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.

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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.onlinejcf.com/article/S1071-9164(22)00076-8/fulltext
# Revised Classification of HF by LVEF

<table>
<thead>
<tr>
<th>HFrEF</th>
<th>HFimpEF</th>
<th>HFmrEF</th>
<th>HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ≤40%</td>
<td>Previous LVEF ≤40% and follow-up measurement of LVEF &gt;40%</td>
<td>LVEF 41-49%</td>
<td>LVEF ≥50%</td>
</tr>
</tbody>
</table>

Evidence of spontaneous or provokable increase LV filling pressures (e.g., elevated NP, noninvasive and invasive hemodynamic measurement)
<table>
<thead>
<tr>
<th>ARNi</th>
<th>BB</th>
<th>MRA</th>
<th>SGLT2i</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recommended in NYHA II-III to reduce M&amp;M</td>
<td>• Metoprolol succinate, carvedilol, or bisoprolol recommended to reduce mortality &amp; hospitalizations</td>
<td>• Recommended in NYHA II-IV to reduce M&amp;M, if eGFR &gt;30 mL/min/1.73m² and serum K &lt;5 mEq/L</td>
<td>• Recommended to reduce HHF and CV mortality, irrespective of the presence of T2DM</td>
</tr>
</tbody>
</table>

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

**Ivabradine (2a)**
- In patients with LVEF ≤ 35% with NYHA II-III; NSR with HR ≥ 70 bpm at rest on maximally tolerated Beta-Blockers.
- Initial dose: 5 mg BID
- Target dose: 7.5 mg BID

**Vericiguat (2b)**
- In patients with LVEF ≤ 45%; recent HFH or IV diuretics; elevated NP levels.
- Initial dose: 2.5 mg QID
- Target dose: 10 mg QID

**Digoxin (2b)**
- In patients with symptomatic HF despite GDMT or unable to tolerate GDMT.
- Initial dose: 0.125-0.25 mg QID (follow monogram)
- Target dose: titrate to achieve serum concentration 0.5-<0.9 ng/ml

**PUFA (2b)**
- In patients with HF and NYHA II-IV
- Dose: 1 gram daily of n-3PUFA (850-880 mg of EPA and DHA)

**Potassium binders (2b)**
- In HF patients with hyperkalemia (≥ 5.5 mEq/L) while taking RAASi.
- Medications: Patiromer; sodium zirconium cyclosilicate

Circulation. 2022;145:00–00. DOI: 10.1161/CIR.00000000000001063
### TABLE 14  Drugs Commonly Used for HFrEF (Stage C HF)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Target Doses(s)</th>
<th>Mean Doses Achieved in Clinical Trials</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACEI</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg 3 times daily</td>
<td>50 mg 3 times daily</td>
<td>122.7 mg total daily</td>
<td>(19)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice daily</td>
<td>10-20 mg twice daily</td>
<td>16.6 mg total daily</td>
<td>(3)</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5-10 mg once daily</td>
<td>40 mg once daily</td>
<td>NA</td>
<td>...</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-5 mg once daily</td>
<td>20-40 mg once daily</td>
<td>32.5-35.0 mg total daily</td>
<td>(17)</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg once daily</td>
<td>8-16 mg once daily</td>
<td>NA</td>
<td>...</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg twice daily</td>
<td>20 mg twice daily</td>
<td>NA</td>
<td>...</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25-2.5 mg once daily</td>
<td>10 mg once daily</td>
<td>NA</td>
<td>...</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg once daily</td>
<td>4 mg once daily</td>
<td>NA</td>
<td>...</td>
</tr>
<tr>
<td><strong>ARB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4-8 mg once daily</td>
<td>32 mg once daily</td>
<td>24 mg total daily</td>
<td>(20)</td>
</tr>
<tr>
<td>Losartan</td>
<td>25-50 mg once daily</td>
<td>50-150 mg once daily</td>
<td>129 mg total daily</td>
<td>(18)</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20-40 mg once daily</td>
<td>160 mg twice daily</td>
<td>254 mg total daily</td>
<td>(21)</td>
</tr>
<tr>
<td><strong>ARNI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril-valsartan (therapy may be initiated at 24 mg sacubitril and 26 mg valsartan twice daily)</td>
<td>97 mg sacubitril and 103 mg valsartan twice daily</td>
<td>182 mg sacubitril and 193 mg valsartan total daily</td>
<td>(22)</td>
<td></td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg once daily</td>
<td>10 mg once daily</td>
<td>8.6 mg total daily</td>
<td>(1)</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>25-50 mg twice daily</td>
<td>37 mg total daily</td>
<td>(23)</td>
</tr>
<tr>
<td>Carvedilol CR</td>
<td>10 mg once daily</td>
<td>80 mg once daily</td>
<td>NA</td>
<td>...</td>
</tr>
<tr>
<td>Metoprolol succinate extended release (metoprolol CR/XL)</td>
<td>12.5-25 mg once daily</td>
<td>200 mg once daily</td>
<td>159 mg total daily</td>
<td>(11)</td>
</tr>
<tr>
<td>Drug Class</td>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mineralocorticoid receptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5-25 mg once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25-50 mg once daily</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>26 mg total daily</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(6)</td>
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<td></td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>SGLT2i</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>10 mg once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10 mg once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.8 mg total daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(8)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Isosorbide dinitrate and hydralazine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed dose combination</td>
<td>20 mg isosorbide dinitrate and 37.5 mg hydralazine 3 times daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 mg isosorbide dinitrate and 75 mg hydralazine 3 times daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90 mg isosorbide dinitrate and ~175 mg hydralazine total daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10)</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-30 mg isosorbide dinitrate and 25-50 mg hydralazine 3-4 times daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>120 mg isosorbide dinitrate total daily in divided doses and 300 mg hydralazine total daily in divided doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NA (24)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>I$_1$ Channel inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>5 mg twice daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.5 mg twice daily</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>12.8 total daily</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(25-27)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Soluble guanylate cyclase stimulator</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verigcuit</td>
<td>2.5 mg once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.2 mg total daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(28)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.125-0.25 mg daily (modified according to monogram)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Individualized variable dose to achieve serum digoxin concentration 0.5-&lt;0.9 ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(29,30)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

*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 nephrilysin 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.

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 included. 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).

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

* p < .005 vs. placebo
** p < .0001 vs. placebo
Carvedilol protocol 220 (MOCHA): six-month crude mortality as deaths per randomized patients×100.

* p<.05 vs. placebo
** p<.001 vs. placebo
# p=.07 vs. placebo


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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.
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

New Recommendations in HFmrEF (LVEF 41-49%)

<table>
<thead>
<tr>
<th><strong>SGLT2i</strong></th>
<th><strong>ARNi, ACEi, or ARB; MRA; BB</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Can be beneficial in decreasing HHF and CV mortality</em></td>
<td><em>May be considered to reduce risk of HHF and CV mortality, particularly among patients with LVEF on lower end of this spectrum</em></td>
</tr>
</tbody>
</table>

2a B-R

2b B-NR

CV, cardiovascular; HHF, hospitalization for HF
New Recommendations in HFpEF (LVEF ≥50%)

**SGLT2i**
- Can be beneficial in decreasing HHF and CV mortality

**MRA**
- May be considered in selected patients to decrease HHF, particularly among patients with LVEF on lower end of this spectrum

**ARNi**
- May be considered in selected patients to decrease HHF, particularly among patients with LVEF on lower end of this spectrum

CV, cardiovascular; HHF, hospitalization for HF
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

IMPORTANCE OF 24-HOUR PHYSICAL BEHAVIORS FOR TYPE 2 DIABETES

SITTING/BREAKING UP PROLONGED SITTING

Limit sitting. Breaking up prolonged sitting (every 30 min) with short regular bouts of slow walking/simple resistance exercises can improve glucose metabolism.

STEPPING

- An increase of only 500 steps/day is associated with a 2.9% decreased risk of cardiovascular mortality and all-cause mortality.
- A 5- to 6-min brisk-intensity walk per day equates to ~4 years’ greater life expectancy.

SLEEP

Aim for consistent, uninterrupted sleep, even on weekends.

Quantity – Long (>8 h) and short (<6 h) sleep durations negatively impact HbA1c.

Quality – Irregular sleep results in poorer glycemic levels, likely influenced by the increased prevalence of insomnia, obstructive sleep apnea, and restless leg syndrome in people with type 2 diabetes.

Chronotype – Evening chronotypes (i.e., night owl; go to bed late and get up late) may be more susceptible to inactivity and poorer glycemic levels vs. morning chronotypes (i.e., early bird; go to bed early and get up early).

SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)

- Encourage ≥150 min/week of moderate-intensity physical activity (i.e., uses large muscle groups, rhythmic in nature) OR ≥75 min/week vigorous-intensity activity spread over ≥3 days/week, with no more than 2 consecutive days of inactivity.
- Supplement with two to three resistance, flexibility, and/or balance sessions.

- As little as 30 min/week of moderate-intensity physical activity improves metabolic profiles.

STRENGTHENING

Physical function/frailty/sarcopenia

- The frailty phenotype in type 2 diabetes is unique, often encompassing obesity alongside physical frailty, at an earlier age. The ability of people with type 2 diabetes to undertake simple functional exercises in middle-age is similar to that in those over a decade older.

Resistance exercise (i.e., any activity that uses the person’s own body weight or works against a resistance) also improves insulin sensitivity and glycemic levels; activities like tai chi and yoga also encompass elements of flexibility and balance.
FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

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

- **ASCVD**
  - Defined differently across CVOs and may include individuals with established CVD (e.g., MI, stroke, any revascularization procedure).
  - Variedly included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

- **Indicators of high risk**
  - Those with a variant phenotype may have a 55% risk of dying at 10 years with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia or albuminuria).

- **HF**
  - Current or prior symptoms of HF with documented HFpEF or HFrEF

- **SGLT2i** with proven HF benefit in this population

- **CKD**
  - eGFR ≤ 45 mL/min per 1.73 m² or albuminuria (AER ≥ 2.0 mg/min per 1.73 m², 10 year).
  - CVD measurements may vary over time, thus a repeat measure is required to document CKD.

- **ASCVD/Indicators of High Risk**

  - GLP-1 RA with proven CVD benefit
  - SGLT2i with proven CVD benefit

  - If HbA1c above target:
    - For patients on a GLP-1 RA consider adding SGLT2i with proven CVD benefit or vice versa
    - T2DM

- **If additional cardiometabolic 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 in a priority in high-risk individuals

  - In general, higher efficacy approaches have greater likelihood of achieving glycemic goals
    - Efficacy for glucose lowering
      - Very High:
        - Darglulide (high dose)
        - Semaglutide, Tirapazide
        - Combination Oral, Cembinial Injectable (GLP-1 RA/Insulin)
      - High:
        - GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD
      - Intermediate:
        - DPP-4
      - Neutral:
        - DPP-4, Metformin

  - When choosing glucose–lowering therapies: Consider regimen with high–to–very high dual glucose and weight efficacy

- **Achievement and Maintenance of Weight Management Goals:**
  - Set individualized weight management goals
  - General Lifestyle advice: medical nutrition therapy/healthy patterns/physical activity
  - Consider medication for weight loss
  - Consider metabolic surgery

* In people with HF, CVD, established CV disease 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 renin–angiotensin system inhibitors. A strong recommendation is warranted for people with HF and a weaker recommendation for those with indications 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 clinical decision-making process. See text for details. * Low-dose TZD may be better tolerated and similarly effective. 5 For SGLT2i, CVD outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HF and renal outcomes in individuals with T2D with established high risk of CV. 4 For T2D, 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 CVD.


**FIGURE 5: PLACE OF INSULIN**

1. Consider immediate start of insulin
   - Severe hyperglycaemia
   - Acute glycaemic dysregulation
   - When T1D is suspected

2. If not already on GLP-1 RA, consider use of GLP-1 RA

3. When not familiar with insulin use or when targets not reached, consider shared care with specialist team

Add mealtime insulin under form of:

- Basal plus
  - (progressive addition of boluses)
- Premixed insulins
- MDI (multiple daily injections)

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# Higher Dose Dulaglutide AWARD 11 Trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A1C Reduction</th>
<th>Weight Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(baseline 8.6 percent)</td>
<td>[baseline 211.4 lbs. (95.9 kg)]</td>
</tr>
<tr>
<td>dulaglutide 4.5 mg</td>
<td>-1.9 percent*</td>
<td>-10.4 lbs. (-4.7 kg)*</td>
</tr>
<tr>
<td>dulaglutide 3 mg</td>
<td>-1.7 percent*</td>
<td>-8.8 lbs. (-4.0 kg)*</td>
</tr>
<tr>
<td>Trulicity 1.5 mg</td>
<td>-1.5 percent</td>
<td>-6.8 lbs. (-3.1 kg)</td>
</tr>
</tbody>
</table>

*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.

<table>
<thead>
<tr>
<th></th>
<th>Trial product estimand</th>
<th>Treatment policy estimand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once-weekly semaglutide</td>
<td>2.0 mg</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>HbA1c reduction</td>
<td>2.2%*</td>
<td>1.9%</td>
</tr>
<tr>
<td>Body weight reduction</td>
<td>6.9 kg*</td>
<td>6.0 kg</td>
</tr>
</tbody>
</table>

*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.

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

<table>
<thead>
<tr>
<th>SURPASS 2 Trial</th>
<th>Semaglutide 1 mg</th>
<th>MOUNJARO 5 mg</th>
<th>MOUNJARO 10 mg</th>
<th>MOUNJARO 15 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Intent-to-Treat (mITT) Population (N)a</td>
<td>468</td>
<td>470</td>
<td>469</td>
<td>469</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.3</td>
<td>8.3</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Change at Week 40b</td>
<td>-1.9</td>
<td>-2.0</td>
<td>-2.2</td>
<td>-2.3</td>
</tr>
<tr>
<td>Difference from semaglutideb (95% CI)</td>
<td>--</td>
<td>-0.2c</td>
<td>-0.4d</td>
<td>-0.5d</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-0.3, -0.0)</td>
<td>(-0.5, -0.3)</td>
<td>(-0.6, -0.3)</td>
<td></td>
</tr>
<tr>
<td>Patients (%) achieving HbA1c &lt;7%e</td>
<td>79</td>
<td>82</td>
<td>86f</td>
<td>86f</td>
</tr>
<tr>
<td>Fasting Serum Glucose (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>171</td>
<td>174</td>
<td>174</td>
<td>172</td>
</tr>
<tr>
<td>Change at Week 40b</td>
<td>-49</td>
<td>-55</td>
<td>-59</td>
<td>-60</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>93.7</td>
<td>92.5</td>
<td>94.8</td>
<td>93.8</td>
</tr>
<tr>
<td>Change at Week 40b</td>
<td>-5.7</td>
<td>-7.6</td>
<td>-9.3</td>
<td>-11.2</td>
</tr>
<tr>
<td>Difference from semaglutideb (95% CI)</td>
<td>--</td>
<td>-1.9c</td>
<td>-3.6d</td>
<td>-5.5d</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-2.8, -1.0)</td>
<td>(-4.5, -2.7)</td>
<td>(-6.4, -4.6)</td>
<td></td>
</tr>
</tbody>
</table>
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 1:1:1:1:1 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
Section 11.

Chronic Kidney Disease and Risk Management
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 m² 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
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).

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.

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.
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
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) 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.

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.
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

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

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>
<thead>
<tr>
<th>Baseline eGFR</th>
<th>Starting finerenone dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\geq 60) mL/minute/1.73 m²</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td>25 to (&lt; 60) mL/minute/1.73 m²</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>(&lt; 25) mL/minute/1.73 m²</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

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  | Starting finerenone dose |
| \(\leq 4.8\) mEq/L             | Increase dose to 20 mg once daily.³ | 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.     | Withhold finerenone.     |
|                                 | Consider restarting at 10 mg once daily when serum potassium \(\leq 5\) mEq/L. | Restart at 10 mg once daily when serum potassium \(\leq 5\) mEq/L. |

³If 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

- CeVD 19.5%
- CAD 69.2%
- PAD 35.2%

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

- No statin 49.9%
- Other statin 27.6%
- High-intensity statin 22.5%

Odds of high (vs other) intensity statin use

More likely
- Male Age
- Age <45
- CAD
- T2DM
- Hypertension
- Cardiology visit

Less likely
- Female
- Age ≥45
- CeVD, PAD
- ↑Charlson comorbidity

Proportion of days covered

- ≥75%: 82.8%
- 50-74%: 10.8%
- <50%: 6.4%

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.

Inclisiran – Leqvio

ORION-11, (NCT03400800) was a multicenter, double-blind, randomized, placebo-controlled 18-month 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%.

---

**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)**

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