New Drugs in Heart Failure

- SGLT2 Inhibitors (e.g., Dapagliflozin, Empagliflozin)
- Sacubitril/Valsartan (Entresto)
- Vericiguat
- Ferric Carboxymaltose
- Goal: Understand mechanisms, benefits, and clinical evidence supporting their use in HF management.

SGLT2 Inhibitors (Dapagliflozin, Empagliflozin)

- Class: Sodium-glucose co-transporter 2 inhibitors
- Mechanism of Action:
- -Block glucose and sodium reabsorption in the proximal renal tubule.
- -Promote glucosuria, osmotic diuresis, and natriuresis → reduce preload and afterload.
- -Improve myocardial energy utilization by shifting toward ketone metabolism.

SGLT2 Inhibitors (Dapagliflozin, Empagliflozin)

- Therapeutic Effects:
- -Decrease cardiac workload and congestion.
- -Improve endothelial function and reduce fibrosis.
- -Renoprotective and anti-inflammatory properties.

- Clinical Evidence:
- -DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved: ↓ CV death and HF hospitalization in patients with or without diabetes.

- Adverse Effects:
- -Genital infections, volume depletion, rare ketoacidosis.

Sacubitril/Valsartan (Entresto)

- Class: Angiotensin receptor –neprilysin inhibitor (ARNI)

- Mechanism of Action:
- -Sacubitril inhibits neprilysin → ↑ natriuretic peptides → vasodilation, natriuresis, anti-fibrotic effects.

- -Valsartan blocks AT1 receptors → ↓ RAAS activation, ↓ vasoconstriction, ↓ aldosterone release.

Sacubitril/Valsartan (Entresto)

- Therapeutic Benefits:
- -Reduces mortality and HF hospitalizations.
- -Improves left ventricular remodeling and function.
- -Enhances quality of life and functional capacity.

- Clinical Trials:
- -PARADIGM-HF: 20% reduction in CV death or HF hospitalization vs. enalapril.
- -PARAGON-HF: Benefit in HFpEF subgroup.

- Safety Considerations:
- -Hypotension, hyperkalemia, renal dysfunction, angioedema.

Vericiguat

- Class: Soluble guanylyl cyclase (sGC) stimulator
- Mechanism of Action:
- -Directly stimulates sGC and sensitizes it to nitric oxide (NO)
- -Increases intracellular cGMP → vasodilation, anti-remodeling, and anti-fibrotic effects.

- Therapeutic Role:
- -Indicated for symptomatic chronic HFrEF patients at high risk after recent decompensation.
- -Improves vascular and myocardial function.

- Clinical Trial:
- -VICTORIA: ↓ CV death or first HF hospitalization in high-risk HFrEF patients.

- Adverse Effects:
- -Hypotension, anemia, syncope.
- -Avoid concomitant use with nitrates or PDE-5 inhibitors.

Ferric Carboxymaltose

- Class: Intravenous iron replacement therapy
- Mechanism of Action:
- -Restores iron stores and hemoglobin synthesis.
- -Enhances oxygen delivery and mitochondrial energy metabolism in cardiac and skeletal muscle.

- Clinical Benefits:
- -Improves exercise tolerance, fatigue, and NYHA class.
- -Reduces HF-related hospitalizations and improves quality of life.

- Key Trials:
- -FAIR-HF, CONFIRM-HF, AFFIRM-AHF: Improved functional capacity and symptoms in iron-deficient HF patients.

- Safety Profile:
- -Generally well-tolerated.
- -Mild hypersensitivity, transient hypertension or headache; rare severe reactions.

New Drugs in Hypertension

New drugs in hypertension

- Aprocitentan: The first approved endothelin receptor antagonist for hypertension, it is used in combination with other agents when blood pressure is inadequately controlled. (Approved 2024).
- Widaplik: This is a single-pill combination of an angiotensin-receptor blocker (telmisartan), a calcium-channel blocker (amlodipine), and a thiazide-like diuretic (indapamide)

Zilebesiran

- Zilebesiran is an investigational RNA interference (RNAi) therapeutic agent that targets designed to selectively silence the AGT gene that provides instructions for making the angiotensinogen protein in the liver.
- By lowering AGT levels, it reduces angiotensin II formation, leading to:

- ↓ vasoconstriction
- ↓ aldosterone release
- ↓ blood pressure

- Because it works upstream in the RAS pathway, its mechanism is more comprehensive than ACE inhibitors or ARBs.

Zilebesiran

Key Features

- Long-acting: A single subcutaneous dose can suppress AGT levels for **months**.
- Potential for twice-yearly dosing, improving adherence in chronic hypertension.
- Does not rely on kidney function for activation, unlike ACE inhibitors or ARBs.

Clinical

Phase 1 and early Phase 2 studies show:

- Sustained reductions in systolic and diastolic blood pressure
- Good tolerability profile
- No major safety signals so far
- **(Still under investigation; not yet FDA-approved.)**