🔑 HEART FAILURE

🔷 1. Frank-Starling Curve

- **CO = HR × SV**
- SV increases with ↑ **preload** (to a certain limit).
- **Too much preload = congestion**, pulmonary edema.
- **Afterload** ↑ = shifts curve **down + right** → ↓ CO
- **Inotropy** ↑ = shifts curve **up + left** → ↑ CO

Drugs mentioned:

- **Preload reduction** is a goal to reduce volume overload in HF.
- **Diuretics**: increase urine output (reduce volume)
- **Venodilators**: reduce venous return to the heart
- **Vasodilators** (e.g., ACE inhibitors): reduce both preload and afterload
- **Inotropes** (e.g., Dobutamine): increase the contractility when the heart can't pump enough on its own

🧠 **Clinical Recall Q:** Why do we use vasodilators in heart failure? 👉 To reduce afterload and improve forward blood flow while also easing the strain on the heart muscle.

🧠 *Key*: More preload ≠ more output always. Overstretch = decompensation.

🔷 2. Pressure-Volume Loop

- **A → B**: Isovolumetric contraction (all valves = close)
- **B → C**: Ejection (LV pressure > aortic pressure) (open aortic valve)
- **C → D**: Isovolumetric relaxation (all valves = close)
- **D → A**: Passive filling (open mitral valve)

🧠 *Important*:

- Stroke volume = EDV - ESV
- ↓ contractility → ↓ ejection → ↑ ESV → **wider, shorter loop**
- ↑ afterload → taller & narrower loop
- Loop shifts reflect cardiac stress.
- In HF, we often see:
  - **Increased EDV** (because the heart can't eject well)
  - **Reduced Stroke Volume**
  - **Shifted loops to the righ**

🔷 3. Initial Compensation in HF

- ↓ contractility = ↓ CO ➔ triggers:
  - **Frank-Starling mechanism:** stretch more, contract more
  - **Neurohormonal activation (SNS + RAAS)**
  - ↑ **Intravascular volume**

🧠 *Short-term = helpful, long-term = destructive* ⚠️ **Eventually, this fails**:

🔷 4. Decompensation

- **Ventricular remodeling** = hypertrophy + dilation
- **Myocyte death/apoptosis** from ischemia/oxidative stress
- **Valvular regurgitation** = stretch → MR, TR

- Ends in ↓ **CO, organ dysfunction, congestion**

🦠 NEUROHUMORAL ACTIVATION

◆ 1. SNS

- ↑ HR, contractility, vasoconstriction
- Chronic activation **➔ beta-receptor downregulation ➔** ↓ sensitivity, ↑ arrhythmia risk
  🛡️ **Treat with: Beta-blockers**

◆ 2. RAAS

- ↓ perfusion → ↑ renin → ↑ Ang II → ↑ Aldosterone
- Results:
  - Na^+/H_2O retention
  - Fibrosis
  - Hypertrophy
  - Vasoconstriction
  - Apoptosis, inflammation
    🛡️ **Treat with: ACEi, ARBs, Spironolactone**

ANGIOTENSIN II EFFECTS

📌 **This slide is a zoom-in on what Angiotensin II does — and it's nasty in HF**:

⚡ **Vascular:**

- **Vasoconstriction** → ↑ BP and ↑ afterload
- **Endothelial dysfunction** → damage to vessel walls

💧 **Hormonal:**

- **↑ Aldosterone** → Na+/water retention
- ↑ Sympathetic drive

💣 **Cardiac/Cellular:**

- **Myocyte hypertrophy** → thicker heart walls
- **Fibroblast proliferation** → scarring
- **Collagen deposition** → stiffness
- **Apoptosis** → myocyte death

🩹 **Others:**

- **Pro-thrombotic** → ↑ risk of clot
- **Pro-oxidant** → oxidative damage

😈 Summary: Angiotensin II turns into a villain in heart failure. That's why ACEIs and ARBs are cornerstone therapies!

◆ 3. Natriuretic Peptides (NPs) 🩶

- *The good guys*: released from heart in overload
- Actions:
  - ↓ SNS
  - Vasodilation
  - Natriuresis
  - ↓ RAAS
  - ↓ hypertrophy/fibrosis
    🛡️ **Boosted by: Sacubitril (ARNI combo)**

🔄 CARDIORENAL SYNDROME

🧠 In heart failure, renal perfusion drops ➤ kidney *thinks* you're hypovolemic ➤ BAD COMPENSATION

🚨 **Results:**

- ↓ **Renal blood flow**
- ↓ **GFR**

- ↑ **Renin** → activates RAAS
- ↑ **Tubular sodium reabsorption**
- ↑ **Vasopressin** → water retention

⛔ This worsens **fluid overload**, raises **preload**, and feeds into the vicious cycle of HF.

🧠 *Vicious cycle where heart and kidney destroy each other*

🧠 **GOLDEN CONCEPTS (Don't ever forget!):**

System	Short Term	Long Term
SNS	↑ CO, BP	Toxicity, arrhythmia, downregulation
RAAS	↑ volume, perfusion	Fibrosis, overload, apoptosis
NPs	↑ natriuresis, vasodilation	**Protective**

💊 **Key Drugs You Must Master:**

Drug	Mechanism	Target
ACEi	↓ Ang-II formation	RAAS
ARB	Block Ang-II receptors	RAAS
Beta-blocker	↓ SNS tone	SNS
Spironolactone	Aldosterone antagonist	RAAS
Sacubitril	Prevent NP breakdown	NPs

🧠 **:**

- **More preload isn't always better.**
- **NPs = protective while SNS & RAAS = destructive when chronic.**
- **Cardiorenal syndrome is a deadly feedback loop.**
- **Block Ang-II = block death.**

🔁 **Ventricular Remodeling after MI**

- After MI, the LV starts expanding, wall thinning, and dilating further.
- This **increases volume** at any pressure = ↓ compliance.
- The weak, stretched wall leads to **worsened EF → progression to HF**.
- ✅ RAAS and sympathetic activation accelerate this process
- ✅ Drugs like ACEIs, ARBs, β-blockers, and MRAs aim to *reverse or slow* remodeling

🫀 **Clinical Findings in HF**

- ↓ Forward output → fatigue, dizziness, hypotension.
- Pulmonary congestion → dyspnea, orthopnea, PND.
- Systemic congestion → edema, ascites, JVD, weight gain.
  🔁 *Cycle*: ↓ contractility → ↓ SV → LV dilation → ↑ filling pressures → congestion.

🩺 **Physical Exam in HF**

- ↓ CO → tachycardia, low BP, cold limbs, narrow pulse pressure, **pulsus alternans** (end-stage).
- Pulmonary: rales (crackles), pleural effusion.

- Cardiac: displaced PMI, **S3** (early filling), MR murmur (due to dilation of LV).
- Systemic: ↑ JVP, hepatosplenomegaly, ascites, peripheral edema.
- **Tip :"LEFT = Lungs, RIGHT = Rest of the body"**

Pearl: S3 = volume overload; displaced PMI = dilation; cool extremities = low perfusion priority to vital organs.

Diagnostic Studies

- **CXR**: cardiomegaly, vascular redistribution, interstitial edema, plural effusion
- **EKG**:can be normal , arrhythmias, LBBB, Q waves.
- **Labs**: BNP (↑ = HF), iron studies (to rule out hemochromatosis), thyroid, ANA+RF , KFT
- **Echo**: wall motion, EF, valve function.
- **Cath**: hemodynamics, coronary anatomy, to asses LVEF
- **Biopsy**: if cause unknown (e.g. myocarditis) or infiltrative diseases (rarely used)

Don't forget: **Echo** = most essential to confirm HF & measure EF.

EF & Prognosis

- ↓ LVEF = **worse survival**.
- It's a major **prognostic marker** in HF.
- Preserved EF = still HF but different management.

Epidemiology & Burden of HF

- Leading cause of admission **>65 years**.
- Huge **financial burden**: 70% of HF costs = hospitalization.

Important: As population ages + post-MI survival improves = HF prevalence ↑.

Economic Impact

- Hospitalization = biggest contributor to cost. , (70% due to hospitalization)/ (10% due to pharmacological tx)

Mortality

- HF has **worse prognosis than many cancers**, especially lung and prostate/breast.
- ~10% mortality after 30 days, ~20% at 1 year, ~40% at 5 years.
  Each admission 4% increases mortality risk.

Progression of HF

- HF is **progressive**.
- With each **acute episode**, QoL ↓, and mortality ↑.
- Chronic decline + acute dips = vicious cycle.

Etiology of HF

- **CHD**: main cause (70%).
- valvular disease (MR/AR) 2nd cause , cardiomyopathies 3rd cause ,
- others: postpartum, chemo-induced, toxins.
- Always think: **ischemia, valves, cardiomyopathy**.

⚠ Comorbidities

- Common: HTN, DM, IHD, arrhythmia, CKD, COPD, anemia.
- HTN → LV hypertrophy → diastolic failure.
- Comorbidities worsen HF & complicate management.

🔁 *Loop*: HTN/DM → LVH → ↓ compliance → HFpEF or HFrEF.

▨ Guideline Development

Level of Evidence	Class of Recommendation
A – multiple RCTs	I – Benefit >>> Risk → SHOULD do it
B – single/small RCTs	IIa – Benefit > Risk → Reasonable
C – expert opinion	IIb – Benefit ≥ Risk → May consider
	III – No benefit or Harm

🧠 **Example:**

- Giving an ACEI to HFrEF patients is: → **Class I, Level A** → Means: **strong evidence, must do it**.

📌 Summary Table:

• I A = Mandatory • IIa B = Good idea, but not bulletproof • III C = Don't waste your time or hurt your patient

💡 *Clinical tip*: Best = A-I. Worst = C-III.

✅ 1. Definition of Heart Failure

- **Clinical syndrome** with symptoms **+ signs**.
- Caused by **structural or functional abnormalities** of the heart → impaired **filling or ejection**.

🔥 *Key concept*: Not just low EF, can be preserved EF but dysfunctional filling.

✅ 2. Symptoms & Signs

- **Symptoms:** Dyspnea, orthopnea, PND, fatigue, leg swelling.
- **Signs:** JVP ↑, gallop S3, displaced apex, murmurs.
- **Acute HF** = sudden onset or worsening of chronic HF.

✅ 3. Classification by LVEF

Type	EF
HFrEF	≤40%
HFpEF	≥50%
Mid-range (HFmrEF)	41–49% (gray zone)

- 🔥 **HFpEF**: preserved systolic function, but diastolic problem (stiff ventricle).
- 🔥 **HFrEF**: systolic dysfunction, dilated ventricle, weak pump.

✅ 4. Subtypes

- **HFpEF** = **concentric hypertrophy**, thick wall, diastolic dysfunction.

- **HFrEF** = **eccentric remodeling**, dilated LV, systolic dysfunction.
- 🔥 *Important:* both can have **diastolic dysfunction** but HFpEF has preserved systolic EF.

✅ 5. Functional Classification (NYHA)

Class	Physical Activity Tolerance
I	No limitation
II	Slight limitation
III	Marked limitation
IV	Symptoms at rest

✅ 6. Stages (AHA/ACCF)

Stage	Definition	NYHA Match
A	High risk for HF, but **no structural heart disease** and **no symptoms**	❌ (No NYHA class)
B	**Structural heart disease**, but **no HF symptoms**	I
C	Structural disease + **past or current HF symptoms**	I, II, III, IV
D	**Refractory HF**, requires **advanced interventions**	IV

✅ 7. Hemodynamic Profile (Warm/Dry system)

	Congested?	Perfused?
Warm & Dry	❌	✅ Best case
Warm & Wet	✅	✅
Cold & Dry	❌	❌
Cold & Wet	✅	❌ Worst case

🔍 **Clinical Examples:**

- **Warm & Dry**: Stable outpatient, well-controlled HF
- **Warm & Wet**: SOB, crackles, edema — but still good BP
- **Cold & Dry**: Cool hands, low BP, sleepy — but no rales or edema
- **Cold & Wet**: ICU patient — fluid overloaded *and* in shock

✅ 8. Symptoms by Side

- **Left-sided HF:** Dyspnea, orthopnea, PND, cough, crackles, blood sputum.
- **Right-sided HF:** JVD, peripheral edema, ascites, hepatomegaly, GI symptoms
- JVD + edema + hepatomegaly = think **right-sided HF** Rales + orthopnea = think **left-sided HF**

✅ 9. Investigations

🧠 **There are 3 core investigations you must do for every HF patient:**

1. ECG (Electrocardiogram)

📚 **ESC Recommendation: Class I, Level C**

🎯 **Purpose:**

- Shows **rhythm** (AF, bradycardia, tachycardia)

- Detects **conduction defects** (e.g., **LBBB** → CRT indication)
- May show **LV hypertrophy** or **Q waves** (old MI)
- **Guides treatment**: e.g., anticoagulation in AF, pacing, CRT

🫀 A normal ECG **almost rules out** HF with reduced EF!

2. Chest X-Ray (CXR)

📚 **ESC Recommendation: Class IIa, Level C**

🎯 **Purpose:**

- Helps rule out **lung disease** as a cause of symptoms
- In HF may show:

Pulmonary venous congestion
Interstitial edema
Pleural effusion
Cardiomegaly

🧠 Remember: "If CXR is clean, don't rush to blame the heart."

3. Echocardiography

📚 **ESC Recommendation: Class I, Level C**

🎯 **The most important test in HF** — gives a full structural & functional assessment:

Shows:

- **Chamber volumes**
- **Wall thickness**
- **Systolic function (EF!)**
- **Diastolic function**
- **Valve status**
- **Pulmonary pressures**

💡 This test confirms the **diagnosis**, classifies the **type**, and directs the **treatment**.

📌 Summary:

"If you suspect HF, get an ECG, a CXR, and an echo — that's your golden triangle. 🛑 No echo? No diagnosis."

✅ 10. BNP vs NT-proBNP (cardiac natriuretic peptides)

. 🧠 **What is BNP?**

BNP = B-type Natriuretic Peptide

- A **32-amino acid** hormone
- Released by **ventricular myocytes**
- Stimulated by **excessive stretch or volume overload**
- Its job = **reduce fluid overload and vascular resistance**

🎯 **Functions of BNP:**

- ↑ **Natriuresis** → more sodium excreted
- ↓ **Vasoconstriction** → more vasodilation
- ↓ **Blood volume** → reduces preload
- ↓ **Sympathetic tone and RAAS activity**

📌 Overall = unloads the heart 🫀

🧪 **BNP vs. ANP:**

- BNP is **ventricular**
- ANP is **atrial**
- BNP has **longer half-life (~20 min)** → More stable to measure in blood

🧠 *BNP got its name because it was first isolated from pig brains ("brain natriuretic peptide")*

🧬 **What is NT-proBNP?**

N-terminal proBNP = the **inactive fragment** co-secreted with BNP

- **76-amino acid** peptide
- **Biologically inactive**
- BUT: has a **much longer half-life (~1–2 hours)** → More reliable marker in labs!

💡 **Clinical Use:**

- Use BNP/NT-proBNP to:
- Diagnose HF in dyspneic patients

- Rule out HF if levels are low
- Track treatment response

Marker	Half-life	Active?	Good for?
BNP	~20 min	✅ Yes	Acute changes
NT-proBNP	1–2 hrs	❌ No	More stable long-term marker

📌 Summary:
"The more your heart stretches, the more BNP it screams out — it's the heart yelling for help."

SYNTHESIS IN MYOCYTES

🧬 **Where is BNP made?**
- Mainly in **left ventricular myocytes**
- Trigger = **increased wall stress/stretch** due to:
- Volume overload
- Pressure overload

⚙️ **Steps of Synthesis:**
- **Pre-proBNP** is made inside the myocyte
- It's cleaved to → **proBNP**
- Then split into:

BNP (32-aa) → biologically **active** hormone
NT-proBNP (76-aa) → **inactive** but used as a **stable biomarker**

💡 **Clinical Insight:**
- More stretch → more BNP/NT-proBNP released
- That's why levels **correlate with severity** of HF
- When treatment works → levels go down 📉

🔬 **Additional Triggers:**
- Not just volume — **ischemia**, **fibrosis**, and **inflammation** also ↑ synthesis

📌 Summary:
"BNP is a stress signal from the ventricles — the more they stretch, the louder they scream

💊 1. ACE Inhibitors (ACEIs)

Examples: Enalapril, Ramipril
Mechanism: Inhibits ACE → ↓ Ang II → ↓ vasoconstriction, ↓ aldosterone
Effect:
✅ ↓ Afterload
✅ ↓ Remodeling
✅ ↑ Survival
Side Effects:

- Dry cough (↑ bradykinin)
- Hyperkalemia
- Hypotension
- Renal dysfunction
- **Angioedema**
  🚫 **Stop if angioedema** (never switch to ARB!)

💊 2. ARBs

Examples: Valsartan, Losartan
Mechanism: Block AT_1 receptors → ↓ Ang II effects
Effect: Same as ACEI but No increase in bradykinin → no cough
Side Effects: Similar to ACEI, **less angioedema and cough**

---

3. Beta Blockers (BBs)

Examples: Bisoprolol, Carvedilol, Metoprolol succinate
Mechanism:

- Block b1 receptors = ↓ HR , renin and remodeling → ↑ filling time
- ↓ sympathetic toxicity
- ↓ myocardial oxygen demand
  Effect:
  ✅ ↓ Mortality (34% in CIBIS-II) and hospitalization
  ✅ Anti-remodeling
  ❌ Must be started **only in stable HF**

Side Effects:

- Bradycardia
- Hypotension
- Cold extremities
- Fatigue
- Sexual dysfunction
- Worsening HF if given too early

Contraindications:
- Acute decompensated HF
- AV block
- Symptomatic bradycardia
- Severe hypotensio

---

4. MRAs – Mineralocorticoid Receptor Antagonists

Examples: Spironolactone, Eplerenone (selective less hormonal side effects)
Mechanism: Block aldosterone receptors →
✅ ↓ Na^+/water retention
✅ ↓ fibrosis
✅ ↓ remodeling
Effect:
✅ ↓ Mortality (30% in RALES)

Indication:
Persistent symptoms in HFrEF (EF ≤35%)

Side Effects:

- Hyperkalemia

- Gynecomastia (spironolactone)
- GI upset

  🚫 Avoid if $K^+ \geq 5$ or GFR < 30

💊 5. Diuretics

Examples: Furosemide (loop|), Bumetanide, HCTZ(thiazides)
Mechanism: Promote natriuresis → ↓ fluid overload
Effect and indications :
✅ Symptom relief ONLY (fluid overload)
❌ No survival benefit
Side Effects:

- Electrolyte loss (↓ K^+, ↓ Na^+)
- Volume depletion
- Hypotension

  🧠 Used **only if congestion** is present

💊 6. Ivabradine

Mechanism: Inhibits **If (funny)** current in SA node → ↓ HR
✅ No effect on contractility
Use:

- HFrEF patients with **HR ≥70–75 bpm** despite BB
- EF< or equals 35 %
- Sinus rythem
-

  Side Effects:
- Visual disturbances (phosphenes)
- Bradycardia

  🧠 Good option if BBs are not tolerated or insufficient

💊 7. Digoxin

Type:
• Cardiac glycoside
Mechanism:
• Inhibits Na^+/K^+ ATPase → ↑ intracellular Ca^{2+} → ↑ myocardial contractility.
• ↑ Vagal tone → slows AV node conduction.
Use in HF:
• For persistent symptoms despite ACEI/BB/MRA
• Especially useful in **HFrEF + AF** (controls ventricular rate)
✅ Improves symptoms ❌ No mortality benefit ✅ ↓ hospitalizations

Used in:
• Sinus rhythm + EF ≤45%
• In patients unable to tolerate BB
• Adjunct to ACEI + MRA in refractory symptoms

→ Not first-line. Add only when core drugs optimized.

Dose:
- 62.5–125 mcg daily

Side effects (toxicity signs):
- GI: Nausea, vomiting, diarrhea
- Cardiac: Arrhythmias, AV block
- CNS: Dizziness, confusion
- Visual: Blurred vision, green/yellow halos
- Rash, eosinophilia (rare)

Increased toxicity risk:
- Hypokalemia
- Renal dysfunction
- Drug interactions (e.g., amiodarone)

Therapeutic level:
- 0.5–0.9 ng/mL (toxic >1.2)

Hydralazine + Isosorbide Dinitrate (H-ISDN)

	⚙ **Mechanism**	💡 **Why it Matters**
	Hydralazine → arterial vasodilator → ↓ afterload	↓ wall stress → easier ejection
	ISDN → venous vasodilator → ↓ preload	↓ congestion → lungs feel lighter
	Combo → ↑ CO & ↓ pulmonary/systemic congestion	

Indications

- 🌍 **African-American** (NYHA III–IV) **on full GDMT**
- 🚫 Intolerance to **ACEI/ARB**
- 🔁 **Persistent symptoms** despite everything else

📊 · H-ISDN – The Facts

🚀 **Dose Titration**	**25 mg 3-4×/day → up to 50-75 mg 4×/day**
⚠ **Side-effects**	Headache, dizziness, flushing, GI upset, tachycardia, hypotension
🔬 **Key Trial**	**A-HeFT** → 43 % ↓ mortality & 33 % ↓ hospitalizations in African-Americans

---

🧠 · Neuro-Hormonal Blockade Trials

Class	Landmark Trial	RRR	ARR
ACE-I	**SOLVD**	16 %	4.5 %
ARB	**CHARM-Alt.**	17 %	3 %
β-Blocker	**CIBIS-II**	**34 %**	5.5 %
MRA	**RALES**	30 %	**11 %**

🏵 *These four pillars built modern HFrEF therapy.*

· ARNI = Sacubitril + Valsartan

Piece	Action	Net Effect
Valsartan	AT_1-blocker	↓ afterload & remodeling
Sacubitril	Neprilysin inhibitor	↑ BNP/ANP → natriuresis & vasodilation

- **PARADIGM-HF** → 20 % ↓ CV death/HF admissions vs. enalapril
- **Indication**: Symptomatic HFrEF who tolerate ACEI (stop ACEI ≥ 36 h before switch)*

· SGLT-2 Inhibitors

Drug Examples	**dapagliflozin, empagliflozin**
Mechanism	Glucuretic + natriuretic → osmotic diuresis, anti-fibrotic
Trials	**DAPA-HF**, **EMPEROR-Reduced** → ↓ death & admissions in diabetics **and** non-diabetics
Caveats	Genital infections, volume depletion, ⚠ avoid GFR < 30 ml/min

---

· Class-of-Evidence Snapshot

Therapy	AHA	ESC	HFSA	NICE
ACEI / ARNI / ARB	**I-A**	**A**	**I-A**	**A**
β-Blocker	**I-A**	**A**	**I-A**	**A**
Diuretics	I-C	A	–	C

→ **MRAs** join core when symptoms persist.
→ **H-ISDN, Ivabradine, Digoxin** = niche or add-on roles.

· 2021 ESC Roadmap for HFrEF (EF ≤ 40 %)

1. **Start ACEI (or better ARNI)**
2. **Add β-blocker** (GDMT dose)
3. **Add MRA**
4. **Add SGLT-2i**

All four = Class I-A.
ACEI → ARNI upgrade when stable (36 h washout).

📐 · Therapy by Stage (A → D)

Stage	Focus	Key Moves
A	Risk	BP, lipids, DM, lifestyle, ACEI in vascular disease
B	Structure, no symptoms	ACEI/ARB/βB ± ICD/repair
C	Symptoms	“Fantastic 4” + diuretics ± digoxin, Ivabradine, H-ISDN, devices
D	Refractory	Inotropes, LVAD, transplant, palliative

🏵️ · ABCD Mnemonic

Letter	Drug	Primary Purpose
A	**ACEI / ARNI**	Neuro-hormonal brake ↓ afterload
B	**β-Blocker**	↓ HR & remodeling
C	**MRA**	Blocks aldosterone (fibrosis)
D	**Diuretic**	Treats congestion (symptom only)

🔁 **Add-ons**: H-ISDN, Ivabradine, Digoxin, CRT/ICD.

⚡ · Left Bundle Branch Block (LBBB)

- **QRS ≥ 120 ms** = definition
- Causes **dyssynchrony** → ↓ EF → 🚪 opens door to **CRT** (esp. QRS ≥ 130 ms).

🛡️ · ICD Essentials

Why?	**Stops VT/VF → saves life (does NOT raise EF)**
Secondary	Prior arrest, sustained VT/VF
Primary	EF ≤ 35 %, NYHA II–III, >40 days post-MI, on GDMT ≥ 3 mo, expected > 1 yr survival

---

♻️ · CRT Benefits

- Synchronizes RV + LV → ↑ **CO**, ↓ **LV volumes**, ↑ **EF**
- Cuts sympathetic surge & admissions
- Most powerful in **LBBB with wide QRS**

✅ · CRT Indications

Must-haves	Details
NYHA II–IV	Symptomatic
EF ≤ 35 %	Systolic failure
Sinus rhythm	For timing
QRS ≥ 130 ms	Prefer LBBB

🚫 *No benefit in narrow QRS or non-LBBB.*

🌟 GOLDEN PEARLS:

- **ACEI/ARB/ARNI + BB + MRA** = Foundation of HFrEF treatment
- **SGLT2i + ARNI** → Latest breakthrough combo
- **BB must be started ONLY when patient is stable**
- **Always check K^+ and Cr before/after starting RAAS blockers**
- **Digoxin is for symptoms—not survival!**

Drug Class	Mechanism	Mortality ↓	Used For	Key Notes
ACEI	↓ Ang II, ↓ aldosterone, ↓ afterload	✅ Yes (SOLVD)	All HFrEF patients unless contraindicated	Causes cough, ↑ bradykinin, angioedema risk
ARB	Blocks Ang II receptors	✅ Yes (CHARM)	If intolerant to ACEI (no cough)	Less angioedema than ACEI
ARNI	↑ BNP (sacubitril), blocks Ang II (valsartan)	✅✅ Strongest	Replace ACEI/ARB if patient stable	Wait 36 hrs after stopping ACEI before starting
BB	↓ HR, ↓ SNS, ↓ remodeling	✅✅ High (CIBIS)	Only in stable HFrEF patients	Don't use in acute decompensation
MRA	Blocks aldosterone, ↓ fibrosis	✅ Yes (RALES)	Add-on if EF ≤ 35%	Monitor K^+ and renal function
SGLT2 inhibitors	Osmotic diuresis, ↓ preload/afterload	✅ Yes	Any HFrEF pt (even without DM)	Prevent hospitalizations
Diuretics	Promote Na^+ & H_2O excretion	❌ No	For symptom relief (congestion, edema)	No mortality benefit
Ivabradine	Inhibits If channel → ↓ HR	❌ No	HR ≥70–75 despite max BB	No inotropy effect
Digoxin	↑ Inotropy, ↓ AV node conduction	❌ No	Symptom control esp. with AF	Narrow therapeutic window
Hydralazine + ISDN	↓ afterload (Hydralazine), ↓ preload (ISDN)	✅ in Blacks (A-HeFT)	Black pts or ACEI/ARB-intolerant	Headache, hypotension common