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PEARLS

- **Heart failure (HF) mortality rate remains high**, as ~50% die within 5 years of diagnosis. Unfortunately, medications known to reduce morbidity & mortality are often underused & underdosed.
- **HFrEF (LVEF ≤40%): strive for quadruple therapy in all patients** (i.e. ❶ ARNI or ACEI or ARB + ❷ HF β-blocker + ❸ MRA + ❹ SGLT2i) to ↓ the risk of death & HF hospitalizations, and improve HF symptoms. Start at low-doses & titrate q1-4 weeks to target or maximally tolerated dose. Refer to Art of Optimizing HF-rEF Medications & drug comparison charts (pages 24-26).
- **Optimizing HFrEF therapy beyond ACEI / ARB + HF β-blocker further reduces the risk of death & HF hospitalizations and improves HF symptoms**. A *few* examples:
  - spironolactone, vs placebo ↓ the risk of mortality **NNT=10** & HF hospitalizations **NNT=11** / 2 years [RALES]
  - **ENTRESTO**, vs enalapril, ↓ the risk of CV death or HF hospitalizations **NNT=21** / ~2 years [PARADIGM-HF]
  - dapagliflozin, vs placebo, ↓ the risk of CV death or worsening HF **NNT=21** / 18 months [DAPA-HF]
- **Tailor additional HFrEF therapies based on individual risk factors**. See column to the right →.
- **Monitor SCr, BUN, eGFR, K^+, & BP** when initiating & titrating ACEI / ARB / ARNI / MRA. An ↑ in SCr of 30%, K^+ ≤5.5mmol/L & asymptomatic SBP 90 to 100mmHg or DBP 50 to 60mmHg is often reasonable.
- **Patients need to play an active role**, particularly with self-monitoring, e.g. daily weights, symptoms, fluid & Na^+ intake. Collaborate on an action plan for new / worsening congestion & when to seek help.

INITIAL WORK-UP

- **Common Clinical Symptoms:** dyspnea, weight gain, edema, fatigue, orthopnea, paroxysmal nocturnal dyspnea, weakness, exercise intolerance, cough, abdominal distention, nocturia, cool extremities
- **Investigations**: chest x-ray, ECG, bloodwork CBC, electrolytes, renal & thyroid function, glucose, NTproBNP or BNP, A1c, urinalysis. If NTproBNP >125pg/mL or BNP >50pg/mL, order ECHO & while waiting start / intensify neurohormonal blocking agents (e.g. ACEI or ARB, HF β-blocker) & encourage lifestyle changes.

HOW IS HEART FAILURE CLASSIFIED? a few examples

Left Ventricular Ejection fraction (LVEF):

- **HF with reduced EF (HFrEF):** LVEF ≤40%
- **HF mildly reduced EF (HFmrEF):** LVEF 41-49%
- **HF with preserved EF (HFpEF):** LVEF ≥50%
- **HF with improved EF (HFimpEF):** baseline LVEF ≤40%, a ≥10% ↑ from baseline, and second measurement of LVEF >40%

HF Symptoms, i.e. New York Heart Association:

- **NYHA class I:** no symptoms
- **NYHA class II:** symptoms with ordinary activity
- **NYHA class III:** symptoms with < ordinary activity
- **NYHA class IV:** symptoms at rest or minimal activity

MANAGEMENT of HF with LVEF >40%

Medications ↓ HF hospitalizations in HFmEF & HFpEF, but not mortality. Use diuretics for congestion. Manage risk factors e.g. HTN, DM, AF & consider LVEF trends; event rates ↓ as LVEF ↑. Consider a SGLT2i (e.g. empagliflozin [EMPEROR-Preserved], dapagliflozin [DELIVER]) [CCS'22 SR, MQ], candesartan [CHARM-P], or spironolactone [TOPCAT CCS'17 WR, MQ]. **ENTRESTO** FDA approved for HFpEF [PARAGON-HF].

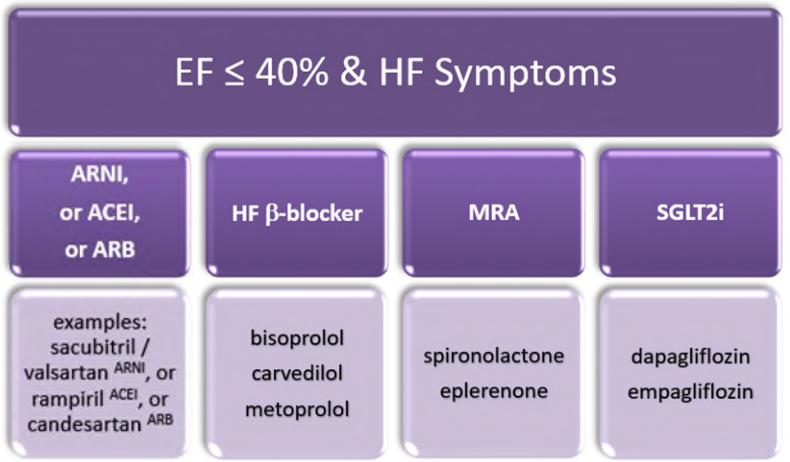
MANAGEMENT of HF with IMPOVED EF

Small studies suggest there is a risk of relapse when HF therapy is stopped; e.g. **TRED-HF**: relapse e.g. ↓ LVEF ≥10% & <50% occurred in 44% of the withdrawal vs 0% control group at 6 months. Continue HF therapy unless not tolerated.

LIFESTYLE

WEIGHT: daily morning weight in the nude & after voiding, especially if fluid retention, congestion, or renal dysfunction; encourage patients to report rapid weight gain (i.e. ~2lbs / 2 days or 5lbs / week)
FLUID INTAKE: limit to 1.5-2L / day if fluid retention or congestion not easily controlled with diuretics, or renal dysfunction or hyponatremia. Consider all liquids e.g. beverages, soups.
SALT INTAKE: no-added Na^+ diet, 2 to 3g salt / day. If advanced HF or ↑ fluid: ≤2g salt / day (~1/4 tsp/d). <1.5g/day did not ↓ clinical outcomes. [SODIUM-HF]
K^+ INTAKE: avoid high-K^+ foods if hyperkalemic
EXERCISE after stress test assessment: improves exercise capacity, symptoms, QOL, ↓ HFrEF hospitalizations. Ideal quantity unknown, but even 15 minutes / day of moderate intensity has benefit.
PATIENT INFO: Heart & Stroke Heart Failure booklet, https://heartlife.ca/, Understanding HF Medications

MEDICATION MANAGEMENT of HFrEF [CCS'21]



Strive to initiate the above agents within 3 to 6 months after diagnosis, and titrate to target or maximally tolerated doses.

OTHER WAYS TO OPTIMIZE / INDIVIDUALIZE HFrEF THERAPY [CCS'21 & '23]

CONGESTION	• use **diuretics** for congestion at any stage • adjust diuretic dose to euvolemic state • combine diuretics if persistent fluid retention (e.g. furosemide + metolazone or acetazolamide) • optimize HFrEF quadruple therapy, e.g. MRA (favoured over K^+ supplement), or agents with diuretic / natriuretic properties (i.e. ARNI, SGLT2i) • refer to RxFiles Furosemide Sliding Scale
SINUS RHYTHM & HR ≥70-77bpm	• add **ivabradine** [SR, HQ, SHIFT] or **digoxin** [WR, MQ, DIG] ↓ HF hospitalizations
BLACK RACE	• add **hydralazine + nitrate** to standard HF therapy in black patients with NYHA III-IV [CCS'21 SR, MQ A-HeFT]
WORSENING HF	• optimize HFrEF quadruple therapy (e.g. beta-blocker [OPTIMIZE-HF], ARNI [PIONEER], SGLT2i [EMPLUSE]) • add **vericiguat** to ↓ HF hospitalizations [CCS'21 CR, MQ, VICTORIA]
ATRIAL FIBRILLATION	• add digoxin [CCS'21 WR, MQ], potentially amiodarone
DE-NOVO HF	• start HFrEF quadruple therapy ASAP; consider starting in pairs (e.g. diuretic + MRA, then ARNI (or ACEI or ARB) + beta-blocker, then SGLT2i)
FRAILITY	• ↓ risk of hypotension & falls by starting with low doses & titrate slowly (q2-4wks), rise slowly from supine to standing, separate administration times, & cardiac rehab
SEVERE HF SYMPTOMS	• refer to cardiologist; acute → ER, chronic → interdisciplinary HF Clinic – if available

ACEI=angiotensin converting enzyme inhibitor **ARB**=angiotensin II receptor blocker **ARNI**=angiotensin receptor-neprilysin inhibitor **β-blocker**=beta-blocker **BNP**=brain natriuretic peptide **EF**=ejection fraction **HFrEF**=heart failure with reduced ejection fraction **LVEF**=left ventricular ejection fraction **MRA**=mineralcorticoid receptor antagonist **NTproBNP**=N-terminal BNP **NYHA**=New York Heart Association **SGLT2i**=sodium glucose co-transporter 2 inhibitor

Generic/TRADE	Initial Dose	HF Target Dose	$/ 30 days	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitoring M	Comments
RAAS INHIBITORS					
Angiotensin Converting Enzyme Inhibitor (ACEI): vs placebo ↓ mortality Meta-analyses NNT=17-27 / ~3yrs, ↓ HF hospitalizations Meta-analysis NNT=20 / ~3yrs, improve HF symptoms CONSENSUS NNT=5					
Captopril CAPOTEN, g 6.25mg, 12.5mg, 25mg, 50mg, 100mg tablet	6.25mg to 12.5mg TID	50mg TID SAVE	$21-38	**CI**: bilateral renal artery stenosis or unilateral if only 1 kidney, pregnancy; **CI** specific to ACEI: history of angioedema **Caution:** K^+ >5.2mmol/L, SCr >220mcmol/L or eGFR <30mL/min, SBP <90mmHg or symptomatic hypotension, moderate to severe aortic stenosis, acute illness SADMANS **DI**: ↑ risk hyperkalemia: K^+ supplements, K^+ sparing diuretics, MRA, renin inhibitors, trimethoprim (e.g. TMP/SMX), NSAIDs, low-salt substitutes high in K^+; ↑ lithium **AE**: angioedema, cough, hyperkalemia, hypotension, renal dysfunction **M**: K^+, BP, SCr & BUN at baseline & 1-2 weeks after initiating or ↑ the dose; note presence / absence of cough at baseline	Benefit of ACEI in HFrEF has been established across a spectrum of HF patients – i.e. those with mild SOLVD Prevention, moderate SOLVD Treatment or severe CONSENSUS HF symptoms, & those with AIRE, SAVE, TRACE or without CAD. **CCS '21 recommend ACEI be used in:** - as part of HFrEF standard therapy unless contraindicated SR, MQ, AIRE, SAVE, SOLVD, TRACE - acute MI with HF or EF <40% post-MI as soon as safely possible post-MI & continue indefinitely SR, HQ, AIRE, SAVE, TRACE **Titration:** double dose q1-3weeks **Which ACEI?** benefit thought to be a class-effect; however, only ACEI with data to support doses are listed here. No compelling evidence to suggest one is better than another.
Enalapril VASOTEC, g 2.5mg^{S}, 5mg^{S}, 10mg^{S}, 20mg^{S} tablet	1.25mg to 2.5mg BID	10mg BID SOLVD; if NYHA class IV: 20mg BID CONSENSUS	$27-31		
Lisinopril PRINIVIL, ZESTRIL, g 5mg^{S}, 10mg, 20mg tablet	2.5mg to 5mg daily	20mg to 35mg daily ATLAS	$18-23		
Ramipril ALTACE, g 1.25mg, 2.5mg, 5mg, 10mg, 15mg$^{X▼}$ capsule	1.25mg to 2.5mg BID	5mg BID AIRE	$14		
Trandolapril MAVIK, g 0.5mg, 1mg, 2mg, 4mg capsule	1mg to 2mg daily	4mg daily TRACE	$19		
Angiotensin II Receptor Blocker (ARB): vs placebo ↓ mortality Meta-analysis NNT=13, ↓ HF hospitalizations Meta-analysis NNT=13, improve HF symptoms VAL-HeFT NNT=42 / ~2years					
Candesartan ATACAND, g 4mg^{S}, 8mg^{S}, 16mg^{S}, 32mg^{S} tablet	4mg to 8mg daily	32mg daily CHARM-Alternative	$17	**CI**, **DI**, **M**, & **AE**: as above with ACEI **Caution:** history of ACEI angioedema **ACEI vs ARB:** incidence of hypotension, renal impairment & hyperkalemia similar; ARBs have ↓ risk of cough & angioedema, but inconsistent mortality benefit	**CCS'21:** recommend ARB in patients intolerant to ACEI (i.e. cough, angioedema) CHARM-Alternative **Titration:** double dose q1-3weeks **Avoid ACEI + ARB** as ↑ risk of hypotension, hyperkalemia, renal dysfunction; instead switch to **ENTRESTO**, &/or add MRA, SGLT2i.
Valsartan DIOVAN, g 40mg^{S}, 80mg, 160mg 320mg tablet	40mg BID	160mg BID VAL-HEFT, VALIANT	$24		
Angiotensin Receptor Blocker Neprilysin Inhibitor (ARNI): vs enalapril ↓ CV death / HF hospitlizations PARADIGM-HF NNT=21 / 2.3years, ↓ HF hospitalizations PARADIGM-HF NNT=36 / 2.3years					
Sacubitril / Valsartan ENTRESTO ☎ ✆ 24mg / 26mg tablet 49mg / 51mg tablet 97mg / 103mg tablet 103mg ENTRESTO = 160mg DIOVAN PARADIGM-HF trial summary	24mg / 26mg BID or 49mg / 51mg BID	97mg / 103mg BID PARADIGM-HF	**$257**	**CI**: concurrent ACEI use (requires a 36-hour wash-out period due to ↑ risk of angioedema), history of ACEI or ARB angioedema **Caution:** recent symptomatic hypotension **DI**, **M**, & **AE**: refer to ACEI / ARB; compared to enalapril, **ENTRESTO** had less elevated K^+ & SCr but more symptomatic hypotension **PARADIGM-HF** excluded CrCl <30mL/min	**CCS'21:** recommend ARNI **in place of ACEI or ARB:** - if remain symptomatic despite HFrEF therapy at appropriate doses SR, HQ, PARADIGM-HF - when hospitalized for acute decompensated HF SR, MQ, TRANSITION, PIONEER-HF - as an alternative to ACEI or ARB in newly diagnosed HF-rEF WR, MQ, TRANSITION, PIONEER-HF **Titration:** double dose q3-6weeks
	Switching from ACEI or ARB → ARNI: • ≥50% of target dose → 49mg / 51mg BID • <50% of target dose or high risk of hypotension → 24mg / 26mg BID ACEI ←→ARNI: 36-hour wash-out period				
Mineralocorticoid Receptor Antagonists (MRA): vs placebo ↓ mortality RALES NNT=10 / 2yrs, EMPHASIS-HF NNT=34 / 21 months, ↓ HF hospitalizations RALES NNT=11 / 2yrs, EMPHASIS-HF NNT=16 / 21 months					
Eplerenone INSPRA, g ☎ ✆ 25mg, 50mg tablet	25mg daily	50mg daily mean daily dose: **EMPHASIS-HF**: 39mg **EPHESUS**: ~43mg	**$80**	**CI**: K^+ ≥6mmol/L; **eplerenone**: Child-Pugh C, strong CYP 3A4 inhibitors e.g. ketoconazole, clarithromycin, ritonavir **Caution:** K^+ >5mmol/L, CrCl <30mL/min **DI**: refer to ACEI above, plus ↑ risk hyperkalemia with ACEI / ARB / ARNI, and - **spironolactone:** ↑digoxin serum levels - **eplerenone:** consider maximum 25mg daily if mild-moderate CYP 3A4 inhibitor e.g. amiodarone, diltiazem, St. John's Wort **AE**: hyperkalemia; **spironolactone:** gynecomastia (dose dependent), erectile dysfunction, menstruation irregularities	**CCS'21 recommend MRA be used in:** - as part of HFrEF standard therapy unless contraindicated SR, MQ, RALES, EMPHASIS-HF - acute MI + EF ≤ 40%, + HF symptoms or DM SR, HQ, EPHESUS **Titration:** q4-8 weeks **Which MRA?** no head-to-head trials; spironolactone studied in moderate to severe HF, RALES vs eplerenone in mild HF. EMPHASIS-HF Eplerenone is not associated with sex hormone AE e.g. gynecomastia but is more costly. **M**: K^+ & SCr baseline & 1 week after initiating & dose ↑, qmonth x 3 months, then q6month
Spironolactone ALDACTONE, g 25mg, 100mg^{S} tablet	12.5mg to 25mg daily	25mg to 50mg daily RALES **RALES**: mean daily dose ~25mg	$5-7		

SADMANS: consider holding SADMANS medications during acute illness (e.g. fever, diarrhea, vomiting) due to concerns of acute kidney injury due to dehydration + certain medications. **S**=sulfonylureas / secretagogues, **A**=ACEI, **D**=diuretics / MRAs / direct renin inhibitor, **M**=metformin, **A**=ARB / ARNI, **N**=NSAIDs, **S**=SGLT2i. See RxFiles SADMANS page for additional info.

Generic/TRADE	Initial Dose	HF Target Dose	$/ 30 days	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitoring M	Comments
HF β-BLOCKER: vs placebo ↓ all-cause mortality Meta-analysis NNT=20 / 11 months, ↓ HF hospitalizations Meta-analysis NNT=18 / 11 months					
Bisoprolol MONOCOR, g 5mg^{S}, 10mg tablet USA: ZEBETA	1.25mg daily	10mg daily CIBIS-II	$10-13	**CI**: in the absence of a pacemaker: 2nd or 3rd degree AV block or HR <50bpm; PR >0.24 sec, severe / uncontrolled asthma, stable COPD is not a CI; severe PAD **Caution**: NYHA class IV, HF exacerbation within 4 weeks can continue current β-blocker unless shock, SBP <90mmHg, HR <50bpm **DI**: bradycardia / AV block risk: verapamil, diltiazem, amiodarone, digoxin; clonidine hypertensive crisis; phenobarbital ↓ β-blocker **AE**: bradycardia, hypotension, fatigue <10%, sexual dysfunction ≤2%, insomnia, vivid dreams, may mask hypoglycemia **M**: HR, BP	**CCS '21** beta-blocker recommendations: - as part of HFrEF standard therapy unless contraindicated SR, MQ, CAPRICORN, CIBIS-II, US Carvedilol Study Group, MERIT-HF, COPERNICUS, MOCHA, ANZ - in LVEF <40% with previous MI SR, MQ - NYHA class IV should be stabilized before initiation of a β-blocker SR, HQ - initiated as soon as possible after HF diagnosis if hemodynamically stable SR, HQ **Titration:** double dose q2-4 weeks, ↓ HR associated with benefit; HF symptoms may get worse before better e.g. transient fluid retention, fatigue. NYHA class III: start with lowest dose. Avoid abrupt withdrawal; taper over 1-2 weeks
Carvedilol COREG, g 3.125mg, 6.25mg, 12.5mg, 25mg tablet	3.125mg BID with food	≤85kg: 25mg bid cc COPERNICUS, COMET >85kg: 50mg BID cc US Carvedilol Study Group	$23-36		
Metoprolol tartrate LOPRESOR, g **SR** (preferred): 100mg, 200mg tablet **Regular:** 25mg^{S}, 50mg^{S}, 100mg^{S} tablet	Regular release: 6.25mg to 12.5mg BID	Regular release: 100mg BID SR: 200mg daily	$19 $21		
Which beta-blocker? The benefit of beta-blockers in HFrEF is not considered a class effect; only bisoprolol, carvedilol & metoprolol are recommended. A few considerations: - Bisoprolol & metoprolol are **cardioselective** → reduce BP less than carvedilol, & may be preferred in DM or reactive airway disease. - **Metoprolol succinate vs tartrate: MERIT-HF** was the first landmark metoprolol trial to show benefit in HFrEF, but it compared metoprolol *succinate* - a long-acting formulation that is not available in Canada, to placebo & had a target dose of 200mg/day. Regular release metoprolol *tartrate* was inferior to carvedilol in the **COMET** trial, but the target dose was 50mg BID. As such, there is limited evidence for short-acting metoprolol tartrate at the recommended target dose. Canadian SR formulation: 100mg & 200mg tablets.					
SGLT2 INHIBITORS: vs placebo in HFrEF ± T2DM ↓ CV death or worsening HF DAPA-HF NNT=21 / 18 months, ↓ CV death or HF hospitalization EMPEROR-Reduced NNT=19 / 16 months					
Dapagliflozin FORXIGA, FARXIGA USA HF: ☎▼, DM: ☎▼ 5mg, 10mg tab (g ✗ ⊗) DAPA-HF trial summary	10mg daily ↓ both CV death & worsening HF DAPA-HF		$100 (g $35)	**CI**: severe renal or hepatic dysfunction **Caution**: hypovolemia, acute illness (hold if dehydrated, i.e. SADMANS) **DI**: diuretics (monitor for hypovolemia) **AE**: if T2DM - genital mycotic infections & euglycemic diabetic ketoacidosis **M**: volume status (if euvolemic → consider ↓ loop diuretic by 30-50%), SCr (early 15% to 20% ↓ in eGFR is acceptable)	**CCS'22 HFrEF:** recommend dapagliflozin DAPA-HF or empagliflozin EMPEROR-Reduced to ↓ all-cause & CV mortality, HF hospitalization, & renal outcomes. SR, MQ **LVEF >40%:** recommend dapagliflozin DELIVER or empagliflozin EMPEROR-Preserved to ↓ HF hospitalization. SR, MQ **Health Canada approval**: empagliflozin for HF, dapagliflozin for HFrEF. **eGFR:** empa ≥20mL/min, dapa ≥25mL/min
Empagliflozin JARDIANCE HF: ✗▼, DM: ☎▼ 10mg, 25mg tablet EMPEROR-Reduced	10mg daily ↓ HF hospitalization EMPEROR-Reduced		$100		
RAISED RESTING HR: vs placebo in HFrEF in sinus rhythm: ivabradine ↓ HF hospitalizations NNT=20 / ~2 years SHIFT, digoxin ↓ HF hospitalizations NNT=13 / 3 years DIG; neither ↓ mortality					
Ivabradine LANCORA, ☎ CORLANOR USA 5mg^{S}, 7.5 mg tablet SHIFT trial summary	2.5mg to 5mg BID with food	7.5mg BID with food SHIFT	$39-118	**CI**: 3rd degree AV block, sick sinus syndrome, pacemaker dependence, prolonged QT, unstable CV conditions, severe renal or hepatic dysfunction **DI**: strong CYP 3A4 inhibitors e.g. ketoconazole, clarithromycin, ritonavir & moderate CYP 3A4 inhibitors that ↓ HR e.g. verapamil, diltiazem are CI; amiodarone, digoxin, simvastatin **AE**: AF, transient flashes of light phosphenes	**CCS'21:** recommend if symptomatic despite guideline therapy at appropriate doses, & resting HR of ≥70bpm, in sinus rhythm, and HF hospitalization within 12 months. SR, HQ, SHIFT **Health Canada** indication HR ≥77bpm based on **SHIFT** subgroup analysis suggesting benefit only applies to patients with this resting HR **Titration**: every 2 to 4 weeks; ↑ if HR >60bpm **M**: HR (target 50-60bpm)
Digoxin TOLOXIN, LANOXIN, g 0.0625mg^{S}, 0.125mg^{S}, 0.25mg^{S} tablet 0.05mg/mL oral solution 0.25mg/mL IV	0.0625mg to 0.25mg daily DIG - Consider **lower doses** (i.e. 0.0625mg to 0.125mg daily) in elderly, BEERS females, or renal impairment - **Loading dose:** not required for HF - **HF target dose:** none - **Levels**: routine levels not recommended. If required, trough or ≥ 8 hrs post-dose. Avoid >1.2ng/mL (1.5nmol/L) in HF ↑ risk of harm. CCS		$17	**CI**: ventricular fibrillation **Caution**: acute MI, AV block, bradycardia, chronic constrictive pericarditis, renal or thyroid dysfunction, hypokalemia **DI**: amiodarone ↓ digoxin dose by 50%, dronedarone, β-blockers, calcium channel blockers, spironolactone, clarithromycin, erythromycin, flecainide, propafenone **AE**: toxicity (anorexia, nausea, vomiting, dizzy, visual changes); overdose: **DIGIBIND**	**CCS'21**: -suggested for HFrEF in sinus rhythm with moderate to severe HF symptoms, despite appropriate doses of guideline therapy to ↓ symptoms & hospitalizations WR, MQ, DIG -suggested for **HFrEF & chronic AF** for rate control, persistent symptoms, or when beta-blockers are not tolerated WR, LQ **M**: HR, SCr caution if CrCL <30mL/min, K^+ hypokalemia ↑ risk of arrhythmia

	Generic/TRADE	Initial Dose	HF Target Dose	$/ 30 days	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitoring M	Comments
HYDRALAZINE / NITRATE	**VASODILATORS:** hydralazine + isosorbide dinitrate (H-ISDN) in **blacks with NYHA III-IV** ↓ mortality NNT=25 / 10 months, ↓ HF hospitalizations NNT=13 / 10 months, & improve QOL A-HeFT					
	Hydralazine APRESOLINE, g 10mg^{S}, 25mg, 50mg tablet	37.5mg TID	75mg to 100mg TID or QID A-HeFT, V-HeFT II	$25-$35	**CI**: acute dissecting aortic aneurysm, mitral valve rheumatic heart disease **DI**: ↓digoxin levels, ↑ metoprolol levels **AE**: hypotension, edema, tachycardia **M**: BP, HR	**CCS'21 recommendations for H-ISDN:** -**in addition** to standard HFrEF therapy at appropriate doses for **black patients** with HFrEF & advanced symptoms SR, MQ, A-HeFT -in patients with HFrEF **who are unable to tolerate an ACEI, ARB, or ARNI** because of hyperkalemia or renal dysfunction Chronic HF: SR, MQ; New-onset HF: WR, LQ; HF hospitalization: WR, LQ; V-HeFT I **V-HeFT II:** H-ISDN similar to enalapril for ↓ risk of all-cause mortality **Titration:** double dose q2weeks, unless AE Nitrate alone may be used to relieve orthopnea, nocturnal or exercise-induced dyspnea, or angina
	Isosorbide dinitrate (ISDN) ISORDIL, g 5mg, 10mg^{S}, 30mg^{S} tablet	20mg TID	40mg TID A-HeFT, V-HeFT II	$26	**CI**: cerebral hemorrhage, severe anemia, severe hypotension or bradycardia, hypertropic obstructive cardiomyopathy **DI**: **CI** sGC stimulators (e.g. vericiguat), within 24 to 48hrs of PDE_5 inhibitors (e.g. sildenafil) **AE**: hypotension, headache, lightheaded **M**: BP, HR 12-hour **nitrate free** interval required to prevent tolerance	
	Isosorbide mononitrate (ISMN) **IMDUR** 60mg^{S} ER tablet	30mg to 60mg daily	Limited evidence with these formulations, but may improve adherence	$22		
	Nitroglycerin NITRODUR, g 0.2, 0.4, 0.6, 0.8mg/hr transdermal patch	0.2mg/hr x 12-hrs		$30		
VERICIGUAT	**Soluble guanylate cyclase (sGC) stimulator:** ↓ CV death or HF hospitalization NNT=34 / 11 months, driven by ↓ HF hospitalizations NNT=46 / 11 months in recently decompensated HF VICTORIA					
	Vericiguat VERQUVO ✗ ⊗ 2.5mg, 5mg, 10mg tablet **VICTORIA** trial summary	2.5mg daily	10mg daily VICTORIA	TBD	**CI**: with other sGC stimulators, i.e. riociguat **DI**: PDE_5 inhibitors (e.g. sildenafil), long-acting nitrates; see **CI** **AE**: anemia, hypotension, syncope **M**: Hgb, BP	**CCS'21:** to be considered in addition to optimal HFrEF therapy in patients with worsening symptoms & HF hospitalizations in the past 6 months CR, MQ, VICTORIA **Titration:** double q2weeks if SBP≥100mmHg

	Generic/TRADE	Initial Dose	Maximum Dose	$/ 30 days	Adverse Events AE / Contraindications CI / Drug Interactions DI / Monitoring M	Comments
LOOP DIURETICS	**DIURETICS:** relieve shortness of breath and edema in HF patients with congestion; do not reduce the risk of mortality					
	Furosemide LASIX, g 20mg, 40mg tablet 80mg tablet ✗ ▼ 10mg / mL oral solution 10mg/mL IV ✗ ⌂	20mg to 40mg daily to BID (e.g. am & noon)	200mg / day	$11-13	**CI**: anuria, in hepatic coma or pre-coma **Caution:** hypokalemia, hyponatremia, eGFR <30mL/min risk of worsening renal function if become hypovolemic, SBP <90mmHg **DI**: risk of digoxin toxicity if diuretic leads to hypokalemia, risk of lithium toxicity due to reduced clearance **AE**: hypotension, volume depletion, gout, ototoxicity with high doses of loop diuretics (e.g. >240mg furosemide) **M**: daily morning weight, baseline & 5-7 days after diuretic adjustments: K^+, Na^+, SCr & urea (↓ / hold diuretic if SCr ↑ >30% from baseline), NTproBNP / BNP; BP **Metolazone or thiazide diuretic or acetazolamide:** consider adding to loop diuretic if diuretic resistance occurs (e.g. ↓ diuretic response over time, failure to ↑ diuresis with ↑ diuretic dose)	**CCS'21:** use diuretics (e.g. furosemide) to relieve congestion, and titrate to minimum effective dose to maintain euvolemia Assess HF symptoms, weight, edema, BP, lab values (electrolytes, renal function, NTproBNP or BNP), fluid & Na^+ intake, & use of medications that can exacerbate HF (e.g. NSAIDs) before adjusting diuretic doses: -**volume deplete / hypovolemic** (e.g. weight below dry weight, decline in renal function): reduce or hold diuretic for 2 to 3 days -**euvolemic** (e.g. dry weight, NYHA class I-II)**:** consider stepwise reduction in diuretic dose or frequency; remember – diuretics can limit titration of HF medications which ↓ mortality -**volume overload / hypervolemic** (e.g. new / worsening HF symptoms, weight ↑): ↑ dose by 25-50% depending on prior response & clinical scenario (e.g. dietary indiscretions) -See RxFiles Furosemide Sliding Scale
	Bumetanide BURINEX ☎ ⊗ 1mg^{S}, 5mg^{S} tablet	0.5mg to 1mg daily	10mg daily	$24-209		
	Ethacrynic acid EDECRIN ☎▼ 25mg^{S} tablet consider if true sulfa allergy to furosemide	25mg to 50mg daily	200mg BID	$41-77		
THIAZIDE-LIKE	**Metolazone** ZAROXOLYN 2.5mg tablet	2.5mg to 10mg every other day to daily (often dosed 30 minutes before furosemide based on onset of action)	20mg daily	$14-25		

Acetazolamide DIAMOX, g: 500mg IV daily + loop diuretic vs placebo ↑ successful decongestion within 3 days & ↓ hospital stay by 1 day.ADVOR 500mg IV vial $120 vs 250mg tab $0.15 (bioavailability 90%).

MEDICATIONS THAT MAY EXACERBATE HF: Na⁺ & water retention: NSAIDs, COX-2 inhibitors, rosiglitazone, pioglitazone, glucocorticosteroids, androgens, estrogens; **cardiotoxic:** ethanol, amphetamine (e.g. cocaine, methamphetamine), carbamazepine, multiple chemotherapy agents; **negative inotropic effect:** antiarrhythmics (amiodarone, disopyramide, dronedarone, flecainide, propafenone, sotalol), non-DHP CCB (i.e. diltiazem, verapamil), itraconazole; **other:** saxagliptin, alogliptin, TNF-α inhibitors (e.g. infliximab). **HERBALS: potentially beneficial herbal**: omega-3 <4g/day, vitamin D or C (if deficient); **potentially harmful herbals**: ginkgo, vitamin E, licorice, grapefruit juice ≥200mL or whole grapefruit within 4 hours of interacting medicatinos (e.g. amiodarone, carvedilol, losartan, sotalol). AHA'23