Chronic Heart Failure (HF)

Improving Outcomes and Preventing Admissions

May 2009

Recent Guidelines:

- Canadian HF Guideline: http://www.chfn.ca/publications 2006[1]; & Updates: 2007[2], 2008[3]; Rt sided HF 2009[4]
- American 2009[5]: http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192065v1
  2005 & Updates: http://www.americanheart.org/presenter.jhtml?identifier=3004550[6] -also: http://www.hfsa.org/
- NICE (UK) 2003[7]: http://www.nice.org.uk/Guidance/CG5
- Europe 2008[8]: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HF-FT.pdf

Review Articles:

- AFP Apr'08: Pharmacologic Management…Systolic Dysfunction: http://www.aafp.org/afp/20080401/957.html
- CMAJ'09 : Diastolic Failure[9]: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2645460

Other Resources:

- http://www.chfn.ca/

Patient Resources:

- http://www.chfn.ca/ under "Patients"
- AFP: http://www.aafp.org/afp/20080401/967ph.html

Highlights: ★

1) Gradually titrate ACEIs & BBs to target doses when possible (mortality benefits)! If low BP, but asymptomatic, push-on!
2) ↓ the dose of diuretics when possible to allow for maximum doses of ACEIs & BBs.
3) If digoxin is used, target levels in the lower end of range (0.6 -1.3nmol/L).
4) Daily weights for monitoring help prevent admissions.
5) Spironolactone is useful in stage 3-4 HF if renal function & K+ status permit.

RxFiles Related:

HF Treatment Overview: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Heart-Failure.pdf

Post-MI Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Post-MI.pdf

ACEI/ARB Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-HTN-ace-arb.pdf

Beta Blocker Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-HTN-bb.pdf

CHARM Trial Overview:
1) ARBs in ACEI Intolerant,
2) ARBs+ACEI, & 3) ARB in PSF
http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHARM-Comments.pdf

see **www.RxFiles.ca**

Systolic HF: Drug Therapy Overview

- About 400,000 people in Canada live with HF. The expected 5 year mortality rate approaches 50%.
- **Systolic HF**: is most common and occurs when the ventricle is dilated and poorly contracting. The left ventricular ejection fraction (EF) is <40%. There is excellent evidence for beneficial treatment options.[10,11]
- See Treatment Overview chart for approach to therapy.

ACE Inhibitors (ACEI) & Beta Blockers (BB): Cornerstones of Therapy to ↓ Mortality

- ACEIs and some BBs have excellent evidence for reducing mortality; however, there may be challenges in achieving and tolerating HF target doses. (See chart!)
- COPD is NOT a contraindication for a cardioselective BB.

Optimal Dosing of ACEI

- ***Start low dose*** (e.g. lisinopril 2.5mg OD; ramipril 1.25mg OD; enalapril 1.25mg BID), especially in those at higher risk of adverse events. Those at higher risk include patients:
  - on high doses of loop diuretics
  - with severe HF (e.g. NYHA class III, IV) or diabetes
  - with low sodium (e.g. <130mmol/L), high creatinine (e.g. >150mmol/L) or low systolic BP (e.g. <120mmHg)
    {A systolic BP of ≥120 indicates lots of room to increase ACEI dose.}
- ***Initiation strategies:***
  - Stop or reduce dose of diuretics for 24 hours
  - Double the ACEI dose at 1 or 2 week intervals until ≥target dose achieved or not tolerated. {e.g. lisinopril 20-40mg OD ATLAS: average 35mg daily better than 5mg daily; ramipril 5mg BID (or 10mg OD); enalapril 10mg BID} In acute HF, may ↑ dose more rapidly e.g. q1-2 days.
  - Check BP, renal function and K+ at baseline, after 1-2 weeks, with any dose increase and periodically thereafter. Expect some rise in BUN, SCr and K+.
- ***Problem Solving: HYPOTENSION***
  - Asymptomatic low BP (e.g. 90/50mmHg) does not usually require any change in therapy.
  - If no symptoms of congestion, reduce diuretic
  - If dizzy, confusion or falls, reassess CCBs, diuretics, ISDN/hydralazine; consider spreading out the administration time of the ACEI from the BB.
- ***Problem Solving:* WORSENING RENAL Fx**
  - A rise in SCr of ≤30% above baseline is acceptable
  - A potassium of ≤5.6 is acceptable
  - Assess for non-essential vasodilators and K+ supplements/diet/retaining agents (e.g. ARBs, spironolactone)
  - Reduce the ACEI dose by half if necessary

Role of ARBs Relative to ACEIs

- ARBs are a good alternative if ACEIs are not tolerated e.g. due to cough.[12] Target dosages are in high end of usual range (e.g. candesartan 32mg OD; see chart). Monitor for worsening renal function as for ACEIs (see above).
- ACEIs and ARBs should not be routinely combined. ARBs may rarely be an add-on option for patients with persistent HF already on a maximally tolerated ACEI dose. Candesartan added to a less than optimal ACEI dose offered some benefit but also increased adverse effects.[13 CHARM-Added] Monitor BP!

Optimal Dosing of Beta Blockers (BB)

- ***Start with low doses!*** (e.g. bisoprolol 1.25mg daily) Initial worsening of HF, hypotension and bradycardia occur with high doses of loop diuretics and those with severe HF. Initiate only if stable HF and euvolemic.
- Increase dose very gradually at 2–4 week intervals, and only if lower doses tolerated. Initial co-administration of diuretics useful in limiting BB induced fluid retention.
- Aim for target dose of a BB that has outcome evidence e.g. bisoprolol 10mg OD; carvedilol 25mg BID; (? metoprolol SR 200mg OD) The benefit of BBs may not be a class effect in HF.
- Monitor clinical status, BP $_{\text{sitting \& standing}}$ & HR
  {HR at rest & after 1 minute of walking may be useful to assess adequacy of β-blockade/BB dose.}

ALREADY ON an ACEI & BB: What's Next!

No other factors	⇨ spironolactone, digoxin; or ARB?, nitrate+/- hydral
Atrial fibrillation	⇨ digoxin (see dosing next page); amiodarone?
Angina	⇨ nitrate*; but may limit ability to up-titrate other meds[14]; (CCBs risky with HF & BB)
Black Race	⇨ nitrate (e.g. ISDN) + hydralazine*[15A-HeFT]
Chronic Renal Avoid spironolactone	⇨ furosemide +/- metolazone 30min pre-loop; ⌖ Nitro patch if tolerated?; ISDN+hydralazine
Congestion {consider also compression stockings}	⇨ loop diuretic or combination of diuretics ⇨ nitro-patch applied at nighttime may be an option for nocturnal dyspnea
High-normal K+	⇨ digoxin or possibly ISDN+hydralazine Avoid: ARBs, spironolactone, NSAIDs
Low-normal K+	⇨ spironolactone or ARB**; Mg^{++} if deficient[16]

*A nitrate + hydralazine combination is only an alternative if not tolerating target doses of ACEI & BB; however, in blacks this combo has evidence for benefit
** Adding an ACEI to an ARB is an option for persistent HF (CHARM trial)[17]; the ONTARGET trial excluded HF patients & did not find additional benefit with telmistartan 80mg plus ramipril 10mg compared to either alone; however, renal dysfunction and hyperkalemia were increased. (See related Q&A.)

Role of Loop Diuretics (e.g. Furosemide)

- Loop diuretics are useful at any stage only if congestion (shortness of breath, edema, fluid retention/↑weight).
  {Tips: may need furosemide BID; thiazide less effective if CrCL <30ml/min.}
- Over-reliance may limit ability to titrate ACEI and BB.

Watch Out With Spironolactone![18]

- Although spironolactone has benefit in stage 3-4 HF[EF <30% RALES], increased K+ can be a problem since patients are usually also on an ACEI (or ARB).[19] Monitor K+ often!
  {e.g. In RALES: q4-wks x3, then q12-wks x3, then q6-monthly}

How low can one let the HR & BP drop when pursuing target ACEI / BB doses?

- Asymptomatic low BP need not change therapy![4]
- A heart rate as low as 50 bpm and a BP as low as 80-90/50 mmHG is reasonable in titrating to target doses.

Which should I add 1st; the BB or the ACEI?

- ACEIs trials came first and the BB trials were done on the background of an ACEI. However BB data shows great mortality benefit. Titrate both at the same time if possible, or maximize one first then onto the next. Delay BB initiation if unstable; otherwise titrate slowly.
- Practically, the ACEI is easier to initiate and titrate with less tolerability concerns. Remember to cut back on diuretic(s) when starting and titrating the ACEI.

HF Considerations in Type 2 Diabetes

- Metformin is 1st line in patients with HF and diabetes if the CrCl is >30ml/min.[1] It has the best outcome data [UKPDS]. In acute HF, dehydration, and worsening or unstable renal function, metformin should be held to prevent lactic acidosis. Monitor CrCl or eGFR q3-6 months or sooner if symptomatic e.g. nausea, vomiting, dehydrated.
- TZDs (rosiglitazone & pioglitazone) ↑ the risk of HF $_{\text{especially systolic}}$
- Cardioselective beta blockers (e.g. bisoprolol) may be preferred when there is significant hypoglycemia risk.
- Caution: potassium retention tends to be problematic in diabetes.

HF Considerations In The Elderly [20]

- HF may present with cognitive impairment, delirium, falls, sleep disturbance, nocturia, and ankle/sacral edema[1]
- Drug therapy approaches are similar but more caution is needed due to higher risk of adverse events e.g.:
  - May require lower starting doses
  - Less likely to achieve target doses of ACEI & BB
  - More prone to electrolyte disturbance therefore caution with spironolactone, diuretic, ACEI/ARB
  - Watch for digoxin toxicity even at therapeutic levels
- BBs appear to maintain beneficial outcomes in the elderly.[21]
- <u>Supine BP</u> should be measured after 5-15 minutes rest
- <u>Standing BP</u> should be measured within 3-5 minutes

{Orthostatic hypotension is defined as: a fall of >20 mmHg SBP or >10 mmHg DBP; present in 1/3 of ≥65yr}

Stopping / Holding of HF Drugs - Caution

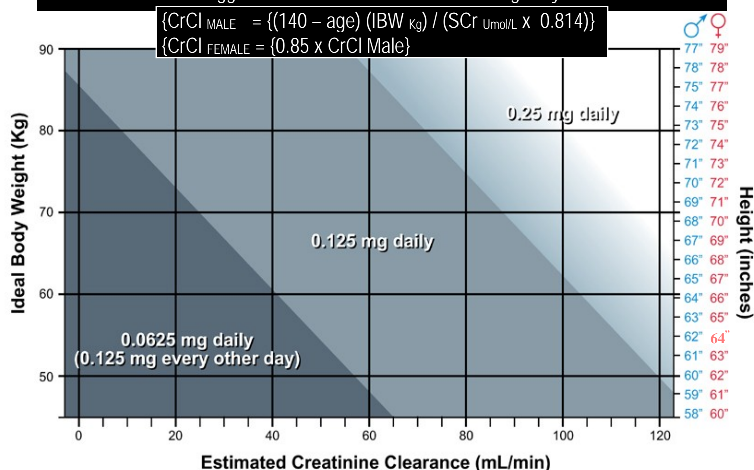
- <u>BB</u> should not be stopped abruptly; taper over 1-2 weeks. If exacerbation of HF, may continue with or decrease BB dose by half if not responsive to other therapy (e.g. ↑ diuretics).
- If <u>ACEI/ARB/BB</u> held in acute illness, restart as soon as possible.

Digoxin Dosing – Aim Low!

- Digoxin is useful as add-on therapy for HF symptoms especially if EF <30% despite optimal doses of ACEI & BB. {Useful for symptom relief, shortening hospital length of stay and increased exercise tolerance; mortality benefit not confirmed.}
  It is also useful in HF patients who also have atrial fibrillation.
- The Bauman Nomogram may be used for initial dosing[22]
- Digoxin benefit in HF may be associated with lower serum levels[23,24]:
  - Post-hoc analysis from the DIG trial found levels <1.0 nmol/L associated with ↓ mortality; levels >1.5nmol/L with ↑ mortality
  - **Digoxin target levels in HF: between 0.6 - 1.3 nmol/L**
- Routine levels not recommended in HF. May do one-time level at 1 month to ensure not supratherapeutic. A level may be useful anytime if toxicity or poor compliance is suspected. If measuring levels:
  - Allow ≥5-10 days after initiating; repeat only if something changes {It may take 15- 20days to reach steady state in renal dysfunction.}
  - Instruct patient & lab to obtain a trough level >8hrs after last dose; this is often taken just prior to the next dose being due.

Figure 1: Bauman Dosing Nomogram: Digoxin Initiation

E.g. for a 75yr woman, 5′3″, 60kg, SCr = 115umol/L & estimated CrCl of 35ml/min, the suggested initial dose would be 0.0625mg daily.



NSAIDs (& COXIBs) & Heart Failure

- All NSAIDs are associated with increased risk in HF[25]
  - Risk is dose dependent, increasing with higher doses
  - Mortality risk may vary for different NSAIDs
    - Very high risk: diclofenac >100mg/day
    - Lower risk: naproxen ≤500mg/day; ibuprofen ≤1200mg/day
    Celecoxib is no better; similar renal effects as other NSAIDs
- **<u>Avoid</u>** NSAIDs including celecoxib in HF patients if possible! {Note: ASA 81mg daily is OK!}
- If needed (e.g. ankle injury limiting activity), limit to short term use.
- <u>Safer analgesic alternatives may include</u>: non-drug measures, acetaminophen, tramadol or opioids; colchicine for gout.

Common Drug Interactions of Concern in HF

<u>ACEI/ARB</u> & allopurinol ↑ hypersensitivity rx, Bactrim ↑K, cyclosporine ↑Scr, digoxin telmisartan ↑ dig, diuretic ↑K if K sparing; ↓BP, lithium ↑ Li level, NSAIDs ↑Scr, ↑BP & spironolactone ↑K.

<u>BB</u> & amiodarone ↓ HR, antidiabetics ↓ hypoglycemic response, ↑BS, CCB ↓BP, worsen HF, clonidine ↑BP-rebound effect if clonidine d/c, cyclosporine ↑cyclo & digoxin ↓ HR, carvedilol ↑ dig.

<u>Digoxin</u> & amiodarone ↑ dig, BB ↓ HR, carvedilol ↑ dig, CCB diltiazem/verapamil ↑ dig, ↑AV block, conazoles itraconazole ↑ dig, cyclosporine ↑ dig, diuretic ↓K may ↑ dig toxicity, erythromycin/clarithromycin ↑ dig, quinidine ↑ dig & spironolactone ↑ dig.

<u>Misc</u>: TZDs & Insulin ↑ fluid volume; Nitroglycerin & sildenafil ↓BP. **<u>Diuretics</u>** with steroids ↓ K.

HF with Preserved Systolic Function (PSF) [26,27,28,29]

e.g. normal ejection fraction (NEF), diastolic dysfunction

- There is a <u>lack of clinical trial data</u> available for significant reduction of mortality and hospitalization with treatments.
- **Maximize management of comorbidities and contributing factors: <u>hypertension</u>** (especially common in elderly females), **<u>heart rate</u>** (& possibly rhythm) in patients with arrhythmias, fluid balance, and myocardial ischemia.
- **Atrial fibrillation** can worsen HF symptoms because of poor rate control and also lack of atrial contribution to cardiac output. Thus a BB +/- digoxin (at the lower HF doses) or possibly amiodarone may be very useful in such patients. If a BB is not tolerated, verapamil or diltiazem may be used for rate control in atrial fibrillation, or angina in PSF patients. {However, verapamil & diltiazem contraindicated if EF <40% and can have adverse drug interactions with digoxin and BBs.}
- BBs may be especially beneficial to slow heart rate, reduce myocardial oxygen demand, lower BP and improve atrial and ventricular filling time. ACEIs may be used cautiously (as with any vasodilator). Benefits have yet to be confirmed in RCTs.
- Irbesartan an ARB was not effective for PSF in I-PRESERVE.[30] Candesartan was not effective in CHARM-Preserved when added to an ACEI, compared to using an ACEI alone.[31]
- Since maintaining preload is essential in PSF, it is important not to overuse diuretics. {However, chlorthalidone 12.5-25mg daily was effective in reducing new-onset HF including PSF [ALLHAT]}[32]
- Benefits of digoxin in PSF are not well established unless used for rate control in atrial fibrillation.

In all patients, don't forget to discuss importance of:

- ***limiting sodium*** *intake (1-3 grams/day depending on congestion/fluid retention)*
- ***limiting fluid*** *intake (1.5-2L/day depending on congestion/fluid retention)*
- ***weighing*** *themselves* ***daily*** *(report gains of >2 lbs in 1-2 days or 5 lbs in 1 wk)*
- ***checking for swelling*** *of the extremities daily*
- ***doing exercise*** *as tolerated (30-45 minutes of aerobic exercise 3-5x / week)*
- ***vaccinations*** *(flu shot yearly; pneumococcal once with possible one time repeat after > 5 years)*
- ***smoking cessation, ASA; statins if otherwise high CV risk***
- ***minimizing alcohol*** *(less than 2-3 drinks/week)* • ***resting*** *when needed*
- ***diet:*** ↑ ***omega-3*** *polyunsaturated fatty acids* • ***advance care directives***
- ***adherence to drug and non-drug treatments*** *(consider need for DVT prophylaxis)*
- ***close observation by pt & medical follow-up when deteriorating HF***
- ***benefits of medications; "live longer and stay out of hospital!"***

<u>Abbreviations</u>: **ACEI**=angiotensin converting enzyme inhibitor **ARB**=angiotensin receptor blocker **BP**=blood pressure **BUN**=blood urea nitrogen **CCB**=calcium channel blocker **EF**=ejection fraction **HF**=heart failure **HR**=heart rate **ISDN**=isosorbide dinitrate **K**=potassium **Scr**=serum creatinine

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Extras:

- **Diltiazem in HF with PSF**: There are no large RCT's or small trials that assess the effect of diltiazem in HF with PSF. There is support for use of diltiazem in atrial fibrillation and hypertension. One very small (n=37) trial assessed IV diltiazem to treat rapid a. fib in patients with moderate to severe HF. No patients had an exacerbation of heart failure.[33] (BB usually preferred initially.)
- **Magnesium in heart failure**[34]: Difficult to fully assess Mg^{++} role in heart failure due to lack of reliable data. Finding an accurate measurement for Mg^{++} stores is difficult. Mg^{++} replacement may be needed to correct K^{+} levels. Low Mg^{++} levels may have a role in arrhythmias & digoxin toxicity. Use caution if using Mg^{++} in patients with renal failure as toxicity may result, leading to cardiovascular (ie-hypotension, arrhythmias, high grade heart block, cardiac arrest), and neurologic (ie:mental status changes) effects.
- **Right sided heart failure**[35]: Right sided heart failure occurs when the right ventricle is dilated & loses its contractility. Decreased function can result in peripheral edema, edema of the visceral organs & ascites. Common causes include left-sided heart failure & pulmonary hypertension, in addition to lung diseases (ie. bronchitis & emphysema), pulmonary embolus, congenital heart disease, & heart valve disease. Treatment includes conventional heart failure treatment (ACEI, BB, & diuretics) & management of the causative mechanism. BB's may be especially poorly tolerated initially, so extra caution on low-dose initiation and titration is critical.
- **Statins & HF:** Many HF patients have other cardiovascular risk factors and will benefit from statin therapy; however, two specific HF trials with rosuvastatin have failed to show clinical outcome benefit (GISSI-HF[36] and CORONA-HF[37]).
- ✥ **Class IV – HF and rising SCr**: CRF (often along with hyponatremia) commonly accompanies Class IV HF, and in this instance the rising SCr often means excessive diuresis and a need for greater cardiac output through afterload reduction. Consider backing off on the diuretics and bumping up the ACE-I or the ARB to 1½ or 2x the recommended dose.

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{See also RxFiles Drug Comparison Chart: Heart Failure: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Heart-Failure.pdf }

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What are the clinical presentations of HF?

⇨**Cardinal triad=FED: Fatigue, Edema, Dyspnea**

⇨**Common**: dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, weakness, exercise intolerance, wt gain, dependent edema, cough, abdominal distension, nocturia, cool extremities

What is the NYHA functional classification?

{NYHA =New York Heart Association; common HF classification}

Class I – No symptoms (Sx)
Class II – Sx with ordinary activity
Class III – Sx with less than ordinary activity
Class IV – Sx at rest or minimal activity

{AHA classification: A:at risk, B:structural but non-symptomatic, C:structural & symptomatic HF, D:refractory HF}

Trivia: *Take it with a grain of salt* (NaCl) [4,5,6,7]

- 1 teaspoonful = ~ 6g of NaCl; ~ 2.4g Na
- Normal diet: 2-3g Na (e.g. >5g salt) per day
- Normal Saline (NS) IV solution = 9g NaCl or 3.6g Na in 1L
  {e.g. NS 0.9% @125ml/hr ⇨10.8g Na (or 27g salt) /3L in 24hr}
- Food/Drink: {Often very high Na^+: bacon, canned soups, condiments, cheese, frozen dinners, lunch meats, pickles, sauces, salted nuts, snacks}
  - 12 oz 360ml Coke/Sprite = 50/70mg Na
  - 1 oz salted pretzels = 150-300mg Na
  - 12 Baked Lays Crisps = 210mg Na
  - 1 cup Cottage cheese = 400-500mg Na
  - 1 Big Mac + 1 Lg Fries (McD) = 1000mg + 450mg Na
  - ⇨ Look for low sodium/serving size e.g. < 170mg Na.

Caution if Na is listed in the first 5 label ingredients!

If hyperkalemia, caution with high K^+ foods

- E.g. apricots, bananas, beans, juices carrot, orange, prune & vegetable, potatoes & tomatoes

Non-pharmacological Management of HF?

Exercise (after Stress Test assessment):

- Regular physical activity is recommended for all patients with stable HF Sx & impaired LV systolic function
- Exercise training 3-5x per wk for 30-45 min/session (include warm-up & cool-down) for NYHA class II - III with LVEF < 40%

Salt, fluid restriction & weight management:

- All HF pts: no-added salt diet (2-3g salt/day).
- Advanced HF & fluid retention: ≤2g salt per day (approx. ¼ tsp/d)
- Daily morning weight nude & after voiding should be monitored in HF, especially with fluid retention, congestion or renal dysfx. Furosemide *sliding scale* may be useful in management of select patients able to adjust dose depending on weight;
  E.g. If rapid 1kg wt ↑, double furosemide dose; if wt ↓1kg hold furosemide.
  {See "Warning Signs & Symptoms" box at bottom of this page.}
- Fluid intake: 1.5-2 L/day for all patients with fluid retention or congestion that is not easily controlled with diuretics, or in patients with significant renal dysfunction or hyponatremia.
  {Fluid intake includes more than just water e.g. soups, puddings, etc.}
- Not more than 1 alcoholic drink per day[3]

For all symptomatic pts with systolic HF:

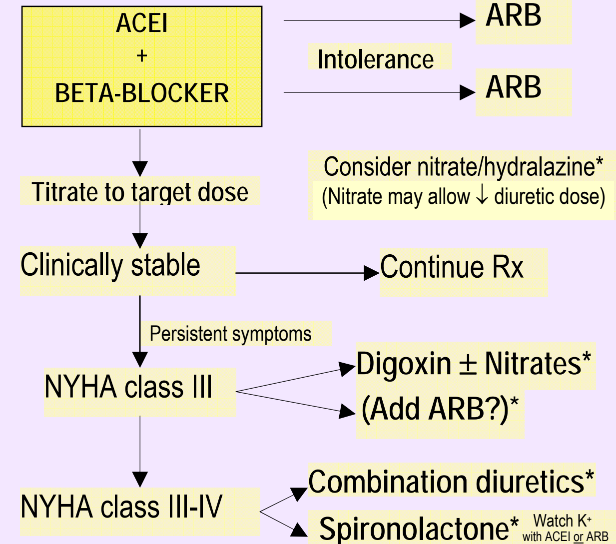
- *Education* {e.g. self-monitoring weight; action plan when to seek help }
- *Aggressive risk reduction (BP, AF, statins, glucose, wt & ASA)*
- *Vaccinations: Influenza annual & pneumococcal one-time*
- *Salt/fluid vigilance; smoking cessation* ● *Tailored diuretic Rx*
- Possibly add fish oils (1g/day n-3 PUFA) GISSI-HF trial: ↓ all-cause death NNT=56 / 3.9yr ;
  {n-3-PUFA = n-3 polyunsaturated fatty acids; Sources: salmon, herring, mackerel & flax.}

What is the treatment management of HF?[1]

- If Sx severe, refer to specialist: acute⇨ER, chronic⇨HF clinic
- If HF Sx & LVEF>40%, treat cause (eg, HTN, ischemia)
- If LVEF ≤ 35%, consider ICD referral; if QRS ≥ 120ms, CRT referral eg. biventricular pacing; If refractory, consider transplant.

If systolic HF LVEF<40%:

Consider diuretic if congestion at any stage, & low-dose ASA 81mg/d if atherosclerosis.



* refer to Drug & Dosage Considerations Chart next page for further considerations on when to use in specific cases.

ACEI=Angiotensin Converting Enzyme Inhibitor **AF**=Atrial fibrillation **ARB**=Angiotensin II Receptor Blocker **BB**=Beta-blocker **BNP**=Brain natriuretic peptide **CRT**=Cardiac Resynchronization Therapy **EF**=Ejection fraction **ER**=Emergency Room **HF**=Heart Failure **HTN**=Hypertension **ICD**=Implantable Cardioverter Defibrillator **LV**=Left ventricle **LVEF**=Left Ventricle Ejection Fraction **Na**=Sodium **NaCl**=Sodium chloride **NYHA**=New York Heart Assoc. **Rx**=Prescription **Sx**=Symptoms **tsp**=teaspoonsful **Tx**=treatment **wt**=weight

Incidence/Prevalence: 1% self-reported HF [1]; 400,000 people in Canada live with HF[1]

- Annual Mortality: 5-50% per year[1]. Up to 40-50% of people with HF die within 5 years of diagnosis[1]
- In 2000, 1.38 million HF associated hospital days; 15.8% died in hospital; ave. hospital stay ~ 13 days[1]

Precipitating Cause: other cardiac (e.g. HTN, CAD, AF, acute MI, valve dx, cardiomyopathy, pericarditis) & non-cardiac (e.g. pulmonary edema or emboli, COPD, ARDS, lung infection); non-adherence (lifestyle, drug tx)

- Acute exacerbations very often avoidable therefore investigate precipitating causes (e.g. *Diet* & *Drugs*)!

Initial Assessment: (When able or appropriate include twelve-lead ECG, chest radiograph & echo)

HISTORY: weakness, fatigue (low-output HF), lightheaded, exercise tolerance change, wheezing, nocturia, orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion; drug exacerbating causes eg. NSAIDs,CCBs, antiarrhythmics

LV involvement: dry cough, ↑weight, cognitive change, pink frothy sputum if severe;

RV involvement: edema, nausea, jaundice {Note: gut edema can dramatically reduce drug absorption.}

PHYSICAL: hepatojugular reflux, edema, ↑JVP, S3 gallop, rales, hepatosplenomegaly; anxiety, sweating, cyanosis

LAB: lytes Ca&Mg, SCr, BUN, LFT, TSH, lipid. (? BNP: may be useful if diagnosis unclear/unexplained dyspnea/risk stratification)

Special Considerations:

- To achieve target doses, systolic BP <100mmHg OK if no hypotension symptoms
- Optimize the role of diuretics in systolic HF. [Note; in diastolic HF, overdiuresis may make HF worse.]
- "Wet beriberi consider if HR > SBP ": ↑↑↑HR & low SBP & 3rd space tendency ⇨high output HF; consider if post-op, or eating poorly x ≥3 mo & getting sicker quite common; may be due to low thiamine, alcohol; Tx Thiamine 100mg od
- If K^+ is low & does not respond to K+ supplement, check Mg^{++} level & supplement if low (250-500mg elemental/day)
  {e.g. Mg^{++} oxide 420mg/tab (=252mg elemental Mg^{++}) 1-2 tab po daily; Mg^{++} glucoheptonate Soln 3g/30ml (=150mg elemental Mg^{++})}

Acute Heart Failure Management:[3]

- Clinical assessment of perfusion (cold/warm) and volume status (wet/dry)
- Initial investigations (CBC, lytes, BUN, SCr, eGFR, troponin, BNP, ECG, chest x-ray, echocardiogram)
- Tx precipitating causes: tachyarrhythmia, ischemia, infection pneumonia,HIV,Hep C, anemia, thyroid dysfx, adherence issues.
- Death risk↑: if ↑SCr, ↓BP systolic, older age, ↑HR, new onset AF, ↓serum Na, anemia, ↓EF, ↑QRS, ↑NYHA class.
- Monitor heart rate, blood pressure, oxygen saturation, response to therapy
- Warm (well perfused, stable BP) & Wet (volume overloaded):
  - IV diuretic congestion (furosemide→double usual PO dose & give it IV, reassess response after 60-90 min & titrate prn), vasodilators (nitroglycerin SL, IV, PO; nitroprusside IV), morphine
- Cold (poor perfusion, hypotensive) and Wet (cardiogenic shock)
  - Positive inotrope [dobutamine 2-5ug/kg/min (preferred) or dopamine or milrinone (0.25ug/kg/min)]
- Once stabilized: consider combined IV diuretics & inotropes, initiate vasodilators (ACEI, hydralazine, nitrates)

PEARLS for ↓ Morbidity & Mortality in HF

(1) Patient education is key (consider referral to interprofessional HF clinic where available).
(2) Make sure ALL patients with reduced EF are on the maximally tolerated dose of a BB & ACEI (or ARB).
(3) After HF controlled, titrate BB dose ↑ gradually (q2-4wks); patient will feel worse before feeling better.
(4) To optimize ACEI & BB doses, consider: ↓ dose of diuretic, nitrates &/or doses of other antihypertensives.
(5) Consider adding a 3rd drug (e.g. spironloactone, digoxin, nitrate) if patient still symptomatic on ACEI + BB.

Warning Signs & Symptoms: ↑shortness of breath esp. with mild exercise, waking up at night with sudden breathlessness, chest pain or discomfort ,↑ fatigue or weakness, swelling in feet/ankles, or rapid ↑ weight {1 kg (2 lbs) in 2days, or 2.5kg (5 lbs) in 7days}

Heart Failure - Drug & Dosage Considerations[1,2]

Prepared by M. Jin, B. Jensen, L. Regier © www.RxFiles.ca May 2009

form/strength g=generic	Start / ⇨Target Dose in Trials	$/30d	PLACE IN THERAPY / COMMENTS / Outcome Evidence / Side effect SE / Contraindication CI

ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)

form/strength g=generic	Start / ⇨Target Dose	$/30d
Ramipril ALTACE, g — 1.25, 2.5, 5, 10, (15✗⊗mg) caps; 2.5 & 5 & 10/12.5mg; 5 & 10/25mg HCT Altace HCT	1.25-2.5mg BID po / ⇨5mg BID - 10mg OD; Max 10mg bid	45-31
Lisinopril ZESTRIL/PRINIVIL, g — 5ˢ, 10, 20mg tab; 10 & 20/12.5mg; 20/25mg tab HCT Zestoretic	2.5-5mg OD po ⇨20-40mg OD ATLAS ave 35mg; Max 20mg bid	35-60
Perindopril COVERSYL, g — 2, 4ˢ, 8 mg tab; 4/1.25mg tab HCT Coversyl Plus	2mg OD po / ⇨4mg OD PEP-CHF 9; Max 4-8mg bid	35
Enalapril VASOTEC, g — 2.5ˢ, 5ˢ, 10ˢ, 20ˢ mg tab; 1.25mg/ml vial; 5mg/12.5mg, 10mg/25ˢ mg tab HCT Vaseretic	1.25-2.5mg BID po / ⇨10mg BID; Max 20mg bid	50
Captopril CAPOTEN, g — 6.25, 12.5, 25ˢ, 50ˢ, 100ˢ mg tab	6.25-12.5mg TID po / ⇨25-50mg TID; Max 50mg qid	67

Start low dose; titrate up as tolerated e.g. Ramipril 2.5mg OD x1wk, 5mg od x 3wk then 5mg BID or 10mg daily Hope. May ↑ dose more quickly e.g. q2days. Aim for max tolerated target dosages!!!

- ✓ ACEI should be used in all pts as soon as safely possible after AMI & continued indefinitely if LVEF < 40 or if AHF complicated the MI [1]
- ✓ ACEI should be used in all asymptomatic pts with a LVEF < 35% & in all pts with Sx of HF & LVEF < 40% [1]
  (ACEI's improve ventricular fx, patient well being, reduces hospital admission for HF & increases survival; appears to be class effect but ACEIs with HF evidence listed)
- **CI**: bilateral renal artery stenosis or unilateral stenosis if only 1 kidney, angioedema, pregnancy. {Some HF clinics may exceed usual max dose.}
- **M**: SCr & K⁺ upon initiation & after 3-7days of starting or adjusting dose (a 30%↑ in SCr & a K⁺ of 5.6mmol/L may be reasonable)
- **SE**: cough<10%, esp. Asians, hypotension/dizzy, ↑K⁺, renal insufficiency. {If ↑SCr >30% in euvolemic pts, consider hydralazine/nitrate combo.}
- **DI**: diuretics K sparing→↑K, lithium↑ levels, NSAIDS↓ effect & potassium↑K; generally avoid combination of ACE+ARB+spironolactone.
- ◆Good evidence for ↓mortality in HF; may use in combo with diuretic (if ↓wt or ↓BP occurs, hold or ↓diuretic dose & maintain ACEI dose)
- ◆ACEI vs. Pl.: All-cause mortality: 15.8% 611/3870 vs. 21.9% 709/3235, NNT=16 [8]; All-cause mortality or Hospitalization for HF: 22.4 vs. 32.6%, NNT=10 [8] META-ANALYSIS
  {Inclusion: patients with symptomatic CHF. Most patients were classified as class II-III at entry. LVEF at entry <0.35 to <0.50}

BETA BLOCKERS (BB) {bisoprolol, metoprolol β_1-selective; carvedilol β_1, β_2 & α_1}

form/strength g=generic	Start / ⇨Target Dose	$/30d
Bisoprolol MONOCOR, g ☎ ▼ — 5ˢ, 10mg tablet [USA: ZEBETA]	1.25mg OD po / ⇨10mg OD Max 20mg/d	21
Carvedilol COREG, g ☎ — 3.125, 6.25, 12.5 & 25mg tab	3.125mg BID po / ⇨25mg BID Max 50mg BID	53
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✝ **Metoprolol SR** LOPRESOR, g — SR: 100mg, 200mg tab (SR form preferred chronically) {Regular 25ˢ, 50ˢ, 100ˢ mg tabs; 10mg/ml susp manufactured at some pharmacies}	12.5-25mg OD po / ⇨200mg SR OD (start with lowest dose if Class III HF) Max 200mg BID	21

{✝Tartrate salt in Canada; but the most studied succinate salt TOPROL XL→only available in the USA; some consider Canadian formulation unproven in HF.}

Start low dose; titrate up as tolerated (~double dose q2-4wks); HF symptoms may get worse before they get better! Aim for maximally tolerated target dosages. If DM/hypoglycemia, bisoprolol or metoprolol may be preferred. {64% of Merit-HF pts reached metoprolol 200mg/d}

- ✓ All HF pts with LVEF ≤40% should receive a BB[1]; If NYHA class IV symptoms, stabilize patient/congestion before initiation of a BB [1]
  (BB's improve ventricular fx, pt well being, ↓ hospitalizations, tx AF & ↑ survival). Avoid abrupt withdrawal! Down-titrate in acute CHF. Caution with IV inotropes & right sided HF.
- **CI**: severe/poorly controlled asthma, 2nd or 3rd degree heart block without a permanent pacemaker, or a PR>0.24sec, symptomatic bradycardia (or HR<50), SBP <85mmHg, decompensated HF,[10] or on cocaine. BB not normally started in pts with symptomatic hypotension despite adjustment of other meds [1]. {Note: Stable COPD is not a CI [1].} Useful for exercise induced ↑HR **M**: HR; SCr, BUN, lytes after 3-7day.
- **SE**: ↓BP, ↓HR, dizziness, fatigue<10%, insomnia, dreams vivid & sexual dysfx ~4%; PAD, cold extremities; hypoglycemia may mask, fluid retention
- **DI**: amiodarone, antidiabetics, CCB synergistic, cimetidine ↑β blocker, clonidine hypertensive crisis, digoxin↓HR, insulins, NSAIDS ↑BP & phenobarbital↓β blocker
- Metoprolol IV CCS-2 trial 11: ↑ cardiogenic shock esp. in those with HF or hypotension. {In severe HF, add low dose inotropes or stop BB.}
- ◆Carvedilol vs. Pl: All-cause mortality: 11.2% 130/1156 vs. 16.8% 190/1133, NNT = 18 in 10.4 months [12] COPERNICUS
- ◆Bisoprolol vs. Pl: All-cause mortality: 11.8% 156/1327 vs. 17.3% 228/1320, NNT=19 in 1.3 years [13] CIBIS II
- ◆Carvedilol 25mg BID vs. Metoprolol 50mg BID (suboptimal: formulation & dose): All-cause mortality: 33.9% 512/1511 vs. 39.5% 600/1518, NNT=18 after 58 months[14] COMET
- ◆Metoprolol CR/XL 200mg CR/XL OD vs. Pl; All cause mortality: 7.2% 217/1990 vs. 11% 237/2001, NNT=28 after 1 year[15] MERIT-HF {This succinate formulation not in Canada}

Angiotensin Receptor Blockers (ARB)

form/strength g=generic	Start / ⇨Target Dose	$/30d
Valsartan DIOVAN — 40ˢ, 80, 160, 320 mg tab; 80/12.5 & 160&320mg//12.5/25mg tab HCT Diovan HCT	40mg BID po / ⇨160mg BID	49/90
Candesartan ATACAND — 4ˢ, 8ˢ, 16ˢ, 32ˢ mg tab; 16/12.5ˢ mg HCT Atacand Plus	4mg OD po / ⇨32mg OD CHARM 22	48/48
Losartan COZAAR — 25, 50, 100mg tab; 50mg/12.5mg HCT tab; 100mg/12.5mg HCT tab; DS =100mg/25mg HCT Hyzaar	→not officially indicated; range 25-100mg OD	50-50

Start low dose; titrate up. Aim for max tolerated dose.

- ✓ ARBs should be used in pts who cannot tolerate ACEI (especially cough), although renal dysfunction & hyperkalemia may occur [1]
- ✓ ARB+ACEI if persistent HF Sx & ↑'d risk of hospitalization despite optimal tx; or when BB contraindicated/not tolerated after careful attempts [1]
- ◆Valsartan vs. Pl: All-cause mortality: 19.7% 495 / 2511 vs. 19.4% 484 / 2499, NS; Hospitalization for HF: 13.8% vs. 18.2% Pl, NNT=23 @23 months [17] Val-HeFT
- ◆Candesartan vs. Pl: CV death: 21.6% 219/1013 vs 24.8% 252/1015, NNT=31; Hospitalization for HF: 20.4% vs 28.2% Pl, NNT=13 @34months[18] CHARM-Alternative
- ◆Candesartan+ACEI vs. Pl: CV death: 23.7% 302 / 1276 vs 27.3% 347 / 1272, NNT=28; Hospitalization for HF: 24.2% vs 28.0%, NNT=26 @41months [19] CHARM-Added
- ◆Losartan 50mg od vs. captopril 50mg tid – NS after 1.5 years[20] ELITE II ◆Irbesartan 300mg od vs. placebo – NS after 49.5mon [21] I-PRESERVE, HF & EF ≥45%, n=4128

Aldosterone Antagonist (for neurohormonal benefit, not just diuretic effect)

form/strength g=generic	Start / ⇨Target Dose	$/30d
Spironolactone ALDACTONE, g	12.5mg OD po / ⇨25mg OD see dose note	8
Eplerenone INSPRA✗⊗ 25,50mg tab NEW Jun09 {?? may have ↓gynecomastia & impotence than spiron.}	25mg od; ↑ to 50mg od @ 4 wks EPHESUS (Post-MI HF); DI with strong CYP3A4 inhibitors e.g. azoles, clarith, PIs; K+ salts	?

- ✓ Option for pts with LVEF <30% & severe HF sx's despite tx optimization, or AHF with an LVEF <30%. (Also useful in right sided HF.) following AMI, if SCr <200umol/L & K⁺ < 5.2 mmol/L [1]. Consider ↓ or discontinue K+ supplements when starting! Counsel re K⁺; Hold if diarrhea.
- **DI**: ↑ K⁺ with ACEI +/or ARB +/or NSAID, ∴ **M**: K⁺ avoid if K+ ≥5mmol/L & renal fx **SE**: gynecomastia, ↑K⁺, ↓Na, rash, menstruation abnormal & ?↑GI ulcers
- All-Cause mortality: 34.5% 284/822 vs. 45.9% 386/841 placebo, NNT=9 after 2 years for severe HF Class III-IV 23 RALES [Note: 50mg/day target dose, but 25mg/day average achieved.]

Vasodilators (Nitrate + Hydralazine used concurrently conventionally)

form/strength g=generic	Start / ⇨Target Dose	$/30d
Isosorbide dinitrate ISORDIL, g — 5mg SL; 10ˢ, 30ˢ mg tabs; 60ˢ mg ER tab IMDUR⊗, g	20mg TID po ac / ⇨40mg TID ac	15/23
Hydralazine APRESOLINE, g — 10ˢ, 25, 50mg tabs; 20mg amp	37.5mg TID po / ⇨75mg TID	35/50

Nitroglycerin patch (0.2, 0.4, 0.6, 0.8mg/hr x12hr) may be ISDN alternative; nocturnal dyspnea.

- ✓ Combination isosorbide dinitrate (ISDN) & hydralazine should be considered in addition to standard therapy for African-Americans with systolic dysfx; also for HF pts unable to tolerate other standard tx[1] & chronic renal failure. {~12hr nitrate free interval prevents tolerance.}
- **CI**: Isosorbide: hypersensitivity; PDE5 inhibitor eg. sildenafil, severe anemia, & shock. Hydralazine: Dissecting aortic aneurysm & rheumatic heart dx mitral valve.
- **SE**: Isosorbide: hypotension, HA, ↑HR, dizzy, flushing & methemoglobinemia; GI upset. Hydralazine: Lupus Sx, ↑HR, HA, edema & peripheral neuropathy.
- ◆All-cause mortality: 6.2% 32/518 vs. 10.2% 54/532 placebo, NNT=25 after 18 months [24] A-HeFT

Diuretics – use IV in acute HF (if gut edema, ↓absorption will make PO route less effective)

form/strength g=generic	Start / ⇨Target Dose	$/30d
Furosemide LASIX, g — 20, 40ˢ mg tabs; 10mg/ml soln; 40 & 250mg vials	20-40mg po OD-BID (Max: 600mg/d)	5-5
Hydrochlorothiazide HYDRODIURIL, g — 12.5, 25ˢ, 50ˢ, (100ˢ✗▼) mg tab - ↓effect if CrCl<30	12.5-25mg po OD-BID (Max: 200mg/d)	5-5
Metolazone ZAROXOLYN 2.5mg tab	2.5-5mg po OD (Max: 20mg/d)	8-14

- ✓ Loops, like furosemide, for most HF pts & congestive Sx. Once ↓acute congestion, use lowest effective dose ? sliding scale for stable S&S[1].
- ✓ For pts with persistent volume overload despite optimal medical therapy & ↑'s in loop diuretics, cautious addition of a 2nd diuretic (eg. a thiazide or low dose metolazone ≥30min pre-loop) may be considered if possible to closely monitor **M**: AM daily weight, Cr, BUN, eGFR, K⁺ ; Mg⁺⁺
- ◆↓/hold diuretic if SCr ↑ >30% from baseline. **DI**: digoxin↑ toxicity if K+ low, ↑ lithium levels, NSAIDs, steroids. **CI**: gout symptomatic hyperuricemia, sulfa allergy?, anuria, ↓ Na+
- **SE**: rash, allergic sulfa rx, photosensitivity rx, ↑ (calcium, uric acid, glucose, cholesterol, TG), ↓ (Na, K⁺ esp. with salbutamol, magnesium, zinc), pancreatitis & sexual dysfx.

Other

form/strength g=generic	Start / ⇨Target Dose	$/30d
Digoxin LANOXIN, g — 0.0625, 0.125ˢ, 0.25ˢ mg tab; 0.05mg/ml elixir; Injectable: 0.25mg/ml amp; 0.05mg/ml amp {Routine levels not recommended in HF[1]; target in HF is ≤1.3nmol/l; (usual range in A.fib 1.3-2.6 nmol/L) In HF, ≥ 1.5 nmol/L associated with harm.[26,27]}	MD: 0.0625 - 0.125mg po OD; Usual Max in HF: 0.25mg po OD; Optional LD: 10ug/kg LBW 0.75-1.25mg PO (eg. 0.5mg IV/po x1, then 0.25mg q6h IV/po x2 doses); {Trough level or at least >8hr post-dose.}	13-13

- ✓ Sinus rhythm pts with moderate-sev persistent Sx despite optimized HF tx, digoxin recommended to ↓Sx esp if EF<30% & hospitalizations[1]
- ✓ Chronic AF pts & poor control of ventricular rate despite BB tx, or when BB cannot be used, consider digoxin [1] Also ↑exercise tolerance.
- **CI**: hypersensitivity, ventricular fibrillation. Caution: acute MI, AV block, chronic constrictive pericarditis, ↓↓ HR, thyroid dx. (DIGIBIND if overdose.)
- **SE / Toxicity**: anorexia, nausea/vomiting, weakness, dizzy, visual change (Digoxin less effective if ↓Ca⁺⁺ or ↓K⁺; but ↑toxic if ↓or↑K⁺, ↑Ca⁺⁺, ↑TSH or ↓Mg⁺⁺)
- ◆No digoxin role in HF pt with preserved LVEF who have normal sinus rhythm [2] **DI**: amiodarone, azoles, CCB, cyclosporine, eryc & quinidine ↑ dig level, BB.
- ◆Digoxin vs Pl: All cause mortality 34.8% vs 35.1%, NS; Hospitalization for HF: 26.8% vs. 34.7%, NNT=13 [25] DIG

Other Meds: Amlodipine (2.5-10mg po daily $30-75) appears to be safe, & may benefit diastolic dysfx & non-ischemic dilated cardiomyopathy. Felodipine (2.5-10mg od $24-32) is an option for systolic HF. Amiodarone 200mg od $50: option in atrial fib & HF. ↑↑SE

☎ = Exception Drug Status in SK ✗ = Non-formulary in SK ✐ =prior approval by NIHB ⊗=not covered NIHB ▼ covered NIHB $=retail cost ˢ=scored tab **ACEI**=angiotensin converting enzyme inhibitor AHF=Acute heart failure AMI=acute myocardial infarction ARB=angiotensin receptor blocker BB=beta blocker BUN=blood urea nitrogen CCB=calcium channel blocker CI=contraindication Cr=serum creatinine CV=cardiovascular eGFR=estimated glomerular filtration rate HA=headache **HCT**=hydrochlorothiazide **HF**=heart failure HR=heart rate K⁺=potassium JVP=jugular venous pressure LBW=lean body weight LD=loading dose LVEF=Left Ventricle Ejection Fraction M=monitor MD=maintenance dose NNT=number needed to treat NS=not significant PAD=peripheral arterial disease Pl=Placebo S&S=signs & symptoms SCr= serum creatinine SE=side effects Sx=symptom TG=triglycerides

For all asymptomatic pts with systolic HF: Education, aggressive risk reduction, lifestyle, salt/fluid vigilance, tailored diuretic Rx. **NOT recommended:** Coenzyme Q10, vitamins, herbal supplements & chelation therapy.

Drugs that ↑ HF: Alcohol, antiarrhythmic amiodarone, disopyramide, dofetilide, ibutilide, flecainide, propafenone, CCB esp. verapamil > diltiazem > nifedipine, glitazones pioglitazone, rosiglitazone, itraconazole, mitoxantrone, **NSAIDs** incl. celecoxib, steroid corticosteroid & anabolic, stimulants cocaine, ephedra, amphetamine & TNF blockers. Chemotherapy: anthracyclines (doxorubicin→dexrazoxane a cardioprotectant; daunorubicin), bleomycin, cetuximab, cyclophosphamide high dose, cytostatic agents, imatinib, interferons, interleukin-2 & trastuzumab.

Brain Natriuretic Peptide (BNP) has diagnostic value for both types of HF and is recommended where available, when diagnosis in unclear. The use of BNP in non-acute HF and community outpatient practice remains to be clarified.[3]

Table: Brain natriuretic peptide (BNP mainly secreted by ventricular myocardium**) & prohormone of BNP (NT-proBNP** longer half life, affected by renal fx**) assay cut-off points for the diagnosis of HF [3]**

	Age	HF unlikely	HF possible but consider alternative diagnoses	HF very likely
BNP (pg/mL)	**All**	**<100**	**100-500**	**>500**
NT-proBNP (pg/mL)	**<50**	**<300**	**300-450**	**>450**
	50-75	**<300**	**300-900**	**>900**
	>75	**<300**	**300-1800**	**>1800**

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