

# Chronic Heart Failure (HF)

## Improving Outcomes and Preventing Admissions

May 2009



### Recent Guidelines:

- **Canadian HF Guideline** : <http://www.chfn.ca/publications> 2006<sup>1</sup>; & Updates: 2007<sup>2</sup>, 2008<sup>3</sup>; Rt sided HF 2009<sup>4</sup>
- **American 2009** <sup>5</sup>: <http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.109.192065v1> 2005 & Updates: <http://www.americanheart.org/presenter.jhtml?identifier=3004550> <sup>6</sup> -also: <http://www.hfsa.org/>
- **NICE (UK) 2003** <sup>7</sup>: <http://www.nice.org.uk/Guidance/CG5>
- **Europe 2008** <sup>8</sup>: <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 <sup>9</sup>: <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) **Spirolactone** 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-arc.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/CHARM-Comments.pdf>  
see [www.RxFiles.ca](http://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. <sup>10,11</sup>
- 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. <sup>12</sup> 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. **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 <sub>sitting & standing</sub> & 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!

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

\*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)<sup>17</sup>; the ONTARGET trial excluded HF patients & did not find additional benefit with telmestartan 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! <sup>18</sup>

- Although spironolactone has benefit in stage 3-4 HF <sup>EF <30%</sup> RALES, increased K+ can be a problem since patients are usually also on an ACEI (or ARB). <sup>19</sup> 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! <sup>4</sup>
- A heart rate as low as 50 bpm and a BP as low as 80-90/50<sub>mmHG</sub> 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 1<sup>st</sup> line in patients with HF and diabetes if the CrCl is >30ml/min.<sup>1</sup> It has the best outcome data<sup>UKPDS</sup>. 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 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<sup>20</sup>

- HF may present with cognitive impairment, delirium, falls, sleep disturbance, nocturia, and ankle/sacral edema<sup>1</sup>
- 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.<sup>21</sup>
- Supine BP should be measured after 5-15 minutes rest
- Standing BP 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

- BB 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 ACEI/ARB/BB held in acute illness, restart as soon as possible.

## Digoxin Dosing – Aim Low!

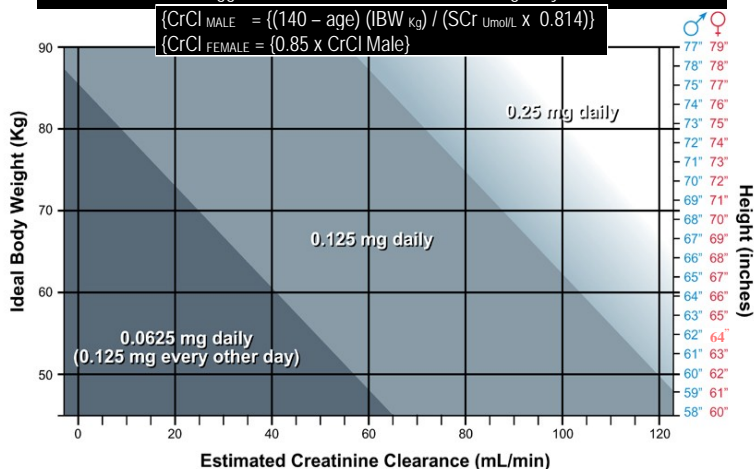
- Digoxin is useful as add-on therapy for HF symptoms especially if EF <30% despite optimal doses of ACEI & BB. (Useful for symptom relief, shortening hospital length of stay and increased exercise tolerance; mortality benefit not confirmed.) It is also useful in HF patients who also have atrial fibrillation.
- The Bauman Nomogram may be used for initial dosing<sup>22</sup>
- Digoxin benefit in HF may be associated with lower serum levels<sup>23,24</sup>:
  - 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 suprathreshold. 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.

$$\{CrCl_{MALE} = \frac{(140 - \text{age}) (IBW_{kg})}{(SCr_{umol/L} \times 0.814)}\}$$

$$\{CrCl_{FEMALE} = (0.85 \times CrCl_{Male})\}$$



## NSAIDs (& COXIBs) & Heart Failure

- All NSAIDs are associated with increased risk in HF<sup>25</sup>
  - 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
- Avoid 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.
- Safer analgesic alternatives may include: non-drug measures, acetaminophen, tramadol or opioids; colchicine for gout.

## Common Drug Interactions of Concern in HF

ACEI/ARB & allopurinol ↑ hypersensitivity rx; Bactrim ↑ K, cyclosporine ↑ Scr, digoxin ↑ telmisartan ↑ dig, diuretic ↑ K if K sparing; \*BP, lithium ↑ Li level, NSAIDs ↑ Scr, ↑ BP & spironolactone ↑ K.  
 BB & amiodarone ↓ HR, antidiabetics ↓ hypoglycemic response, ↑ BS, CCB ↓ BP, worsen HF, clonidine ↓ BP-rebound effect if clonidine d/c, cyclosporine ↑ cyclo & digoxin ↑ HR, carvedilol ↑ dig.  
 Digoxin & 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.  
 Misc: TZDs & Insulin ↑ fluid volume; Nitroglycerin & sildenafil ↓ BP. Diuretics with steroids ↓ K.

## HF with Preserved Systolic Function (PSF)<sup>26,27,28,29</sup> e.g. normal ejection fraction (NEF), diastolic dysfunction

- There is a lack of clinical trial data available for significant reduction of mortality and hospitalization with treatments.
- Maximize management of comorbidities and contributing factors: hypertension (especially common in elderly females), heart rate (& 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.<sup>30</sup> Candesartan was not effective in CHARM-Preserved when added to an ACEI, compared to using an ACEI alone.<sup>31</sup>
- 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.}<sup>32</sup>
- 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!"

Abbreviations: 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



## 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.<sup>33</sup> (BB usually preferred initially.)
- **Magnesium in heart failure**<sup>34</sup>: Difficult to fully assess Mg<sup>++</sup> role in heart failure due to lack of reliable data. Finding an accurate measurement for Mg<sup>++</sup> stores is difficult. Mg<sup>++</sup> replacement may be needed to correct K<sup>+</sup> levels. Low Mg<sup>++</sup> levels may have a role in arrhythmias & digoxin toxicity. Use caution if using Mg<sup>++</sup> 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**<sup>35</sup>: 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<sup>36</sup> and CORONA-HF<sup>37</sup>).
- **♣ 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.

## References – RxFiles Newsletter : Heart Failure (2009)

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

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