Angiotensin Converting Enzyme Inhibitors (ACEIs) / Angiotensin Receptor Blockers (ARBs)*

Heart Failure Medication Initiation and Titration

Initiation

Symptomatic HF or LVEF < 40%

Bilateral renal artery stenosis
Moderate/Severe aortic stenosis
Hyperkalemia: K+ > 5.5 mmol/L
Renal Dysfunction: Serum Creatinine > 220 µmol/L
Hypotension: SBP < 90 mmhg or symptoms
Allergy: angioedema, hives, rash
Intolerance: cough (ACE)

- NO → **Considerations:**
  - Baseline cough
  - K+ supplements
  - K+ sparing diuretics
  - Spironolactone
  - NSAIDs/COX2 inhibitors
  - Combination ACEI/ARB
  - → **See dosing section (reverse)**
  - → **See monitoring section**
- YES → **Refer to Physician**

Titration

Titrate every 1-3 weeks, depending on tolerance

Goal: Target dose (see dosing) or maximum tolerated dose

Hypotension
SBP < 90 mmHg with symptoms*
**Watch for trends*

→ **Fluid Assessment**

- **Volume deplete** → Reduce/hold diuretic x 2-3 days → No improvement, hold/reduce ACEI/ARB x 1-2 wks & reassess
- **Euvolemic** → Reassess diuretic dose/vasodilator
- **Volume overload** → Reduce/hold dose of other vasodilators +/- ACEI/ARB x 1-2 weeks → **See Diuretic algorithm** → Reassess 1-2 wks

Assess

- **BP**
- **K +**
- **Scr**

Hyperkalemia
K+ > 5.2 mmol/L*
**Watch for trends*

Considerations:
- Dietary K+
- K+ supplements
- K+ sparing diuretics
- Spironolactone
- Combo ACEI/ARB
- Renal Dysfunction

- **K+ 5.2-5.5** → Stop K+ supplements, reduce/hold spironolactone → Serum K+ in 3-5 days, Reassess ACEI/ARB dose
- **K+ 5.6-6.0** → Stop K+ supplements, spironolactone, hold ACEI/ARB → Serum K+ in 2-3 days, Reassess ACEI/ARB dose
- **K+ > 6.0** → **Refer to Physician**

Renal dysfunction
>30% in serum creatinine*
**Watch for trends*

Considerations:
- Addition of nephrotoxic drugs (NSAIDS/COX2)
- Worsening HF
- Co-morbidity interplay

→ **Fluid Assessment**

- **Volume deplete** → Reduce/hold diuretic x 2-3 days → Scr in 5-7 days
- **Euvolemic** → Hold ACEI/ARB → Scr in 5-7 days → **Re-challenge at lower dose**
- **Volume overload** → Increase diuretic; reduce/hold of ACEI/ARB → Scr in 2-3 days

Monitoring **

Initiation of ACEI/ARB	Blood Pressure	Serum Creatinine	Serum Potassium
• Baseline Scr / GFR • Baseline K+ • Baseline blood pressure	Every Visit	1 week after: 1) initiation 2) dosage increase* 3) > 30% ↑ in Scr	1 week after: 1) initiation 2) dosage increase*

*Obtain baseline value prior to any up-titration or change in symptom status

If stable: Q 3-6 months

Other considerations:

Angioedema:
- Stop ACEI/ARB, contact physician
- Do not rechallenge
- Caution when substituting ARB for ACEI

Cough:
- Assess cough at baseline or if due to worsening HF
- If intractable cough secondary to ACEI consider:
- Trial of another ACEI
- Switch to ARB

Reassess in 2 weeks and document

*This algorithm is intended for single agent (ACEI or ARB)

**This is a guide to monitoring; increased monitoring may be required given patient's status and co-morbidities (i.e. renal insufficiency)

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Drug	Initial Dose	Target Dose[1]	Dosage forms (mg)
ACEIs[2]			
Captopril[3] (generic)	12.5mg tid	50mg tid	12.5, 25, 50, 100
Cilazapril (Inhibace®, generic)	2.5mg qd	10mg qd	1, 2.5, 5
Enalapril (Vasotec®, generic)	2.5mg bid	10mg bid	2.5, 5, 10, 20
Fosinopril (Monopril®, generic)	10mg qd	40mg qd	10, 20
Lisinopril (Prinivil®, Zestril®, generic)	2.5mg qd	30-40mg qd	5, 10, 20
Perindopril (Coversyl®)	2mg qd	4-8mg qd	2, 4, 8
Quinapril (Accupril®)	5-10mg qd	40mg qd	5, 10, 20, 40
Ramipril (Altace®, generic)	1.25-2.5mg bid	5mg bid	1.25, 2.5, 5, 10
Trandolapril (Mavik®)	0.5-1mg qd	4mg qd	0.5, 1, 2, 4
ARBs[4]			
Candesartan (Atacand®)	4mg qd	32mg	8, 16
Valsartan (Diovan®)	40mg bid	160mg bid	80, 160

[1]Target doses based on clinical trials, but are limited to patient tolerance
[2]ACEIs are first line agents
[3]Limited use due to TID dosing
[4]ARBs are second line. Agents listed have been used and studied in clinical trials

Key points:
-**ACEIs are first line treatment for NYHA Class I-IV**
-ARBs are considered second line agents when an ACEI is not tolerated secondary to a **cough** and rarely **angioedema**
-Cough should be assessed and clearly documented **prior to** initiation of ACEI
-If cough is determined to be secondary to ACEI use (e.g. resolves upon discontinuation or recurs on re-challenge), and is bothersome enough to warrant reassessment of therapy, it should be documented
-If titration of dose is limited by **hypotension**:
  -reassess diuretic use
  -consider staggering dosing with other vasoactive agents or dosing at bedtime
-Compliance is increased with once daily dosing strategy
-Given that the main side effects of ACEIs and ARBs are **renal dysfunction** and **hyperkalemia**, assessment of other medications and factors that precipitate these effects are warranted:
1) Renal dysfunction: NSAIDs and COX2 inhibitors
2) Hyperkalemia: combination therapy, spironolactone, potassium supplements, potassium-sparing diuretics (triazide, Dyazide, triamterene, amiloride), salt substitutes (No Salt, Half Salt), dietary K+

•Goal is to keep patient at target or maximally tolerated dose of evidence based medications
•Clinical course of HF is variable—frequent reassessment of medication regime required
•Complete and thorough history and physical assessment essential with each dose adjustment
•Titrate one medication at a time—small dose changes may result in significant clinical ones (ie. symptoms, BW)

April 2012

Beta - Blockers

Heart Failure Medication Initiation and Titration

Initiation

LVEF < 40%

Bifascicular block PR interval prolongation (>0.24 msec)
Bradycardia: HR < 60 bpm or symptomatic 2nd or 3rd degree AV block without a pacemaker
Hypotension: SBP < 90 mmHg or symptoms
Asthma
Acute decompensated heart failure
Intolerance or allergy

NO → **Considerations:**
- COPD with reversible component
- Other rate controlling drugs:
  - CCB*: verapamil, diltiazem
  - amiodarone
  - sotalol
  - digoxin

→ **See dosing section (reverse)**
→ **See monitoring section**

YES → **Refer to Physician**

Titration

Titrate every 2-4 weeks, depending on tolerance

Goal: Target dose (see dosing) or maximum tolerated dose

Hypotension SBP < 90 mmHg with symptoms →

Considerations:
Other BP lowering drugs:
- vasodilators (nitrates, hydralazine, CCB)
- ACEI
- diuretics

- **Volume deplete** → Reduce/hold diuretic x 2-3 days
- **Euvolemic** → Reassess diuretic dose vasodilator dose, other BP lowering drugs → No improvement, hold/reduce BB x 1-2 wks reassess
- **Volume overload** → See below (volume overload)

Assess

- **BP**
- **Heart Rate**
- **Fluid Status**

Bradycardia HR < 55 bpm with symptoms →

Considerations:
Other rate controlling drugs:
- diltiazem, verapamil
- sotalol
- amiodarone
- digoxin

→ **Conduction Abnormality?**
- Bifascicular block
- PR interval prolongation
- 2nd or 3rd degree AV block

- **NO** → Consider decreasing BB dose Reassess in two weeks
- **YES** → Stop BB Consider referral to Cardiologist

Volume overload →

Considerations:
Other precipitants of fluid retention:
- NSAIDs, glitazones
- Salt/fluid intake
- Non compliance
- Co-morbidity
- Worsening HF

- Mild symptoms → Maintain BB dose Increase diuretic Sodium/fluid restriction → **See Diuretic algorithm**
- Moderate to severe symptoms → Consider reducing BB dose Increase diuretic Sodium/fluid restriction

Monitoring **

Initiation of BB	Blood Pressure	Heart Rate	Fluid Status
• Baseline ECG • Baseline heart rate • Baseline blood pressure	Every Visit	Every Visit ECG as clinically indicated: • after each up-titration • Δ in symptom status	Every visit patient should be instructed to perform daily weights

*verapamil and diltiazem are contraindicated in systolic heart failure (EF < 40%)
**This is a guide to monitoring; increased monitoring may be required given patient's status and co-morbidities

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Drug	Initial Dose	Target Dose[1]	Dosage forms (mg)
BetaBlockers[2]			
Bisoprolol* (Monocor®, generic)	**1.25mg daily**	**10mg daily**	**2.5, 5, 10**
Carvedilol (Coreg®, generic)	**3.125mg bid**	**25mg bid**	**6.25, 12.5, 25**
Metoprolol tartrate[3]* (Lopressor®, generic)	**6.25-12.5mg bid**	**100mg bid**	**25, 50, 100**

[1]Target doses based on clinical trials, but are limited to patient tolerance
[2]Agents are considered first line supported with clinical trials
[3]Clinical trials used CR/XL (metoprolol succinate) formulation, but not available in Canada. Metoprolol tartrate long acting available in 100mg and 200mg strengths only.
** Beta-selective: preferred in airway disease*

Patient counseling tips:

- BB may worsen HF symptoms initially (particularly fatigue), but in long run will improve symptoms
- BB are started at low dose, titrated slowly to minimize adverse effects
- Self-monitoring for symptoms is key
- Daily weights are important; call your health care provider if your weight increases by:
  2-3 lbs in 1-2 days or 5 lbs in 1 week
- Stopping high dose BB abruptly may result in a rapid HR, exacerbation of HF symptoms—titrate dose down when possible

Key points:

-**BBs are first line treatment for NYHA II-IV HF**

-*Gradual titration of dosing is important to prevent HF exacerbations and improve tolerability*
  - fluid assessment is very important
  - titrate doses by 50-100% as tolerated every 2-4 weeks—individualize to patient
  - avoid reducing diuretic doses (unless adverse effects i.e. dehydration) while up-titrating
  - BB may be considered in patients with recent HF exacerbations as long as they are stable and euvolemic

-Compliance is increased with once daily dosing

-Consider beta-selective agents in airway disease*

-Given that the main side effects of BBs are **hypotension**, and **bradycardia,** assessment for reduction / sacrifice of other non mortality / morbidity reducing medications that precipitate these effects is warranted:

1) Hypotension: nitrates, antihypertensive agents, hydralazine, diuretics
2) Bradycardia: digoxin, verapamil, diltiazem, amiodarone, dronedarone

•Goal is to keep patient at target or maximally tolerated dose of evidence based medication
•Clinical course of HF is variable—frequent reassessment of medication regime required
•Complete and thorough history and physical assessment essential with each dose adjustment
•Titrate one medication at a time, small dose changes may result in significant clinical ones (i.e. symptoms, HR)

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Diuretics

Heart Failure Medication Initiation and Titration

Initiation

Heart failure with signs and symptoms of fluid overload*

Fluid Assessment
Worsening / new SOB
Worsening SOBOE
Recent weight gain**
Peripheral pitting edema
Orthopnea / PND
Sacral edema / Ascites
JVP assessment-JVD
Hepatojugular reflex
Pulmonary edema: rales, crackles, CXR

Considerations:
- Fluid restriction (1-1.5L/d)
- Sodium restriction (<2gm/d)
- Underlying renal dysfunction
- History of past diuretic use
- Non adherence
- Other precipitants: NSAIDs, glitazones, increase BB dose
- Sodium load
- Worsening HF/Co-morbidity

See dosing section (reverse)

See monitoring section

Titration

Titrate **up, down or maintain** according to symptoms
Goal: Minimum dose to achieve euvolemia; *dose should be reassessed each visit*

Hypotension SBP < 90 mmHg with symptoms

Fluid Assessment

- **Volume deplete** → Reduce/hold diuretic x 2-3 days & reassess maintenance dose 3-7 days
- **Euvolemic** → Reassess diuretic dose/vasodilator
- **Volume overload** → Increase diuretics/stagger dose Reduce/hold dose of other vasodilators +/- ACEI/ARB x 1-2 wks

Assess

- **Fluid Status**
- **Blood Pressure**
- **K+**
- **SCr**

Hypokalemia
K+ < 3.5 mmol/L*
**Watch for trends*

Considerations:
- K+ supplementation
- Addition of ACEI/ARB
- Spironolactone
- Renal function

Consider K+ Supplementation → **Fluid Assessment**

- **Volume deplete** → Reduce/hold diuretic x 2-3 days & assess maintenance dose 3-7 days
- **Euvolemic** → Reassess diuretic dose

Renal dysfunction
>30 % ↑ in serum creatinine*
**Watch for trends*

Considerations:
- Addition of ACEI/ARB
- Spironolactone
- Nephrotoxic drugs: NSAIDs, COX2
- Worsening HF

Fluid Assessment

- **Volume deplete** → Reduce/hold diuretic x 2-3 days → Scr in 5-7 days
- **Euvolemic** → Reassess diuretic dose → Scr in 5-7 days
- **Volume overload** → Consider reduce/hold dose ACEI/ARB → Scr in 2-3 days

Monitoring**

Indication of Diuretic	Fluid Assessment	Serum Creatine	Serum Potassium	Blood Pressure
• Baseline Scr / GFR • Baseline K+ • Baseline blood pressure	Every Visit	1 week after: 1) initiation 2) dosage increase** 3) > 30 % ↑ in SCr	1 week after: 1) initiation 2) dosage increase**	Every Visit

**Obtain baseline value prior to any up-titration or Δ in symptom status

*Common signs and symptoms include new and worsening shortness of breath, weight gain, HF cough, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, ascites
**Weight gain: 2-3 lbs in 1-2 days or 5 lbs in 1 week
**This is a guide to monitoring; increased monitoring may be required given patient's status and co-morbidities

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Drug	Initial Dose*	Maximum Daily Dose	Dosage forms (mg)
Loop Diuretics			
Furosemide (generic, Lasix®)	20-40mg OD-BID	200mg (caution > 120mg)	20mg, 40mg
Bumetanide (Burinex®)	0.5-1.0mg OD-BID	10mg	1mg, 5mg
Ethacrynic Acid (Edecrin®)	50-100mg	400mg (200mg BID)	25mg
Thiazide Diuretics			
Metolazone (Zaroxolyn®)	2.5mg daily	20mg	2.5mg
Hydrochlorothiazide (generic)	____	____	____
Indapamide (generic, Lozide®)	____	____	____
Chorthalidone (generic)	____	____	____
Potassium-sparing Diuretics			
Spironolactone (generic, Aldactone ®)	12.5-25mg	25mg	25mg, 100mg
Amiloride (generic)	____	____	____
Triamterene (generic)	____	____	____

*Doses of commonly used agents in heart failure listed only. All agents listed to indicate which agents have diuretic effects. Note that mild diuretic can be used in those with minimal fluid retention.

Key points:

-Diuretics are for **symptomatic relief—*should never be used alone***

-**Goal of treatment**—fluid balance control at the ***minimum effective dose***

-Regular fluid assessment is key

-Encourage **daily weights** to monitor shifts in fluid balance

-If titration of dose is limited by **<u>hypotension</u>**:

-reassess diuretic use

-consider staggering dosing with other antihypertensives or dosing at bedtime

Other adverse effects:

-**Electrolyte disturbances**: ↓ K+ (except K+ sparing), Mg+, Na+, Ca++ (except thiazides)

- ↑ **uric acid** may predispose patients to gout attacks

- Combination antihypertensive products which include diuretics—avoid combinations of multiple diuretic agents.

-**<u>If non-responsive consider:</u>**

- adherence

- increase sodium intake

- NSAID / COX2 use

- renal dysfunction (may requiring higher doses)

•Clinical course of HF is variable—frequent reassessment of medication regime required

•Complete and thorough history and physical assessment essential with each dose adjustment

•Small dose changes may result in significant clinical ones (i.e. symptoms, BW)

April 2012

Spironolactone/Eplerenone
Heart Failure Medication Initiation and Titration

Initiation

Symptomatic heart failure (NYHA III-IV or high risk NYHA II*) on ACEI/BB and LVEF < 35%

Hyperkalemia:
K+ > 5.2 mmol/L

Renal dysfunction:
Serum creatinine > 220 µmol/L
or a creatinine clearance
< 30 ml/min

NO → **Considerations:**
- K+ supplements
- K+ sparing diuretics
- NSAIDs/COX2 inhibitors
- ACEI or ARB

→ **See key points**

→ **See monitoring section**

YES → **Refer to Physician**

Titration

Titrate monthly depending on tolerance

Goal: Target dose (see dosing below) or maximum tolerated dose

Hyperkalemia
K+ > 5.2 mmol/L*
**Watch for trends*

Considerations:
- K+ supplements
- K+ sparing diuretics
- Dietary K+
- ACEI or ARB
- Renal dysfunction

K+ 5.2-5.5 → Stop K+ supplements, Reduce/hold spironolactone → Serum K+ in 3-5 days

K+ > 5.5 → Stop K+ supplements, Hold spironolactone Reduce/hold ACEI/ARB Refer to physician → Serum K+ in 2-3 days

Assess

- **K +**
- **Scr**

Renal Dysfunction
> 30 % ↑ in SCr*
**Watch for trends*

Considerations:
- Addition of nephrotoxic drugs: NSAIDs/ COX2
- ACEI or ARB

Fluid assessment

Volume deplete → Reduce/hold diuretic x 2-3 days → Scr in 5-7 days

Euvolemic → Reduce/hold spironolactone → Scr in 5-7 days → Consider re-challenge at lower dose

Volume overload → Reduce/hold spironolactone → Scr in 2-3 days

Monitoring **

Initiation of Spironolactone	Serum Creatinine	Serum Potassium
• Baseline Scr / GFR • Baseline K+	• After initiation: 3 days, 1 week, 4 weeks, then monthly x 3 • Prior to any up-titration of Spironolactone, ACEI, or ARB • 1 week post up-titration of Spironolactone, ACEI, or ARB • With dehydration, illness, or change in symptom status	

- *Goal is to keep patient at target or maximally tolerated dose of evidence based medications*
- *Clinical course of HF is variable—frequent reassessment of medication regime required*
- *Complete and thorough history and physical assessment essential with each dose adjustment*
- *Titrate one medication at a time—small dose changes may result in significant clinical ones (i.e. symptoms, BW)*

Key Points

- **Spironolactone therapy is indicated in patients with LVEF < 35 % and NYHA III-IV HF**
- ***Eplerenone therapy is indicated in high risk NYHA II [aged >55 years and LVEF ≤30%, or LVEF ≤35% and QRS duration >130 ms] and recent hospitalization for HF or elevated BNP/NT-proBNP levels**
- **DOSING:** The usual dose is 50 mg daily, however, those with poor renal function and/or a history of hyperkalemia should be initiated on 12.5 mg daily and titrated as tolerated. *NOTE: Average doses achieved in clinical trials for spironolactone and eplerenone were 26mg and 40mg respectively.*

- Triple therapy with ACEI + ARB + spironolactone should be avoided
- Recent evidence has documented significant issues with hyperkalemia and renal dysfunction and warrants close clinical monitoring
- Stop K+ supplementation and other K+ sparing diuretics at initiation of spironolactone
- Should be on max. medical therapy including ACEI/ARB prior to initiation

Other considerations: Gynecomastia (4-5% of males) with spironolactone

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