MOH CLINICAL PHARMACY PRACTICE GUIDELINES

Management of Chronic Heart Failure

MINISTRY OF HEALTH
SINGAPORE

Chapter of Cardiologists
College of Physicians, Singapore

October 2007

Clinical Pharmacy Practice Guidelines

Management of Chronic Heart Failure

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Published by:
Ministry of Health, Singapore
16 College Road,
College of Medicine Building
Singapore 169854

Printed by:
Oxford Graphic Printers Pte Ltd

ISBN: 978-981-05-9116-8

Statement of Intent

The contents of this publication are guidelines for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each healthcare professional is ultimately responsible for the management of his/her unique patient in the light of clinical data presented by the patient and the diagnostic and treatment options available.

FOREWORD

The prevalence of heart failure amongst Singaporeans is expected to increase due to our ageing population. Heart failure is a chronic disease which results in high mortality rates. Early intervention and treatment help to delay the progression of the disease.

In several restructured hospitals, ambulatory management of heart failure is carried out in an outpatient heart failure clinic staffed by a multidisciplinary team that includes pharmacists. In overseas countries, the establishment of such heart failure clinics have resulted in better patient outcomes.

These guidelines provide up-to-date recommendations on the management of heart failure patients. The focus of these guidelines is on the pharmacological management of heart failure patients. A section on the management of co-morbid conditions in heart failure and a brief overview of non-pharmacological management of heart failure patients has also been included.

These guidelines will be an important reference to pharmacists practising in outpatient heart failure clinics. It will also be useful to other healthcare professionals concerned with the care of patients with heart failure.

I would like to congratulate the workgroup for coming up with these guidelines.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

Contents

1 INTRODUCTION

Heart failure is a clinical syndrome that can result from any disorder that impairs the ability of the ventricle to fill with or eject blood, thus rendering the heart unable to meet the metabolic demands of the body.[1] It is a chronic, progressive disease that is characterised by frequent hospital admissions and ultimately, high mortality rates.

Heart failure is a major public healthcare concern in Singapore, especially in our ageing population. Between 1st October 2005 and 30th September 2006, there were 4,332 cases of heart failure admitted to restructured hospitals in Singapore alone. These patients had an average length of stay of 5.4 days, and a median bill size of between $444 and $2,992.50.[2] Early intervention and treatment to prevent decompensation may delay disease progression and improve survival. After the initial diagnosis and implementation of standard medical therapy, outpatient management of heart failure focuses on stabilising the patient. Patient education, which includes promotion of compliance and smoking cessation among others, may further contribute to clinical stability and improved patient outcomes.[3]

Multidisciplinary outpatient heart failure clinics have been the focus of many centres in the United States, as well as several countries in Europe. These have been proven to improve patient outcomes, including reduced heart failure symptoms, improved quality of life, reduced hospital re-admission rates, as well as reduced healthcare costs.[4, 5, 6, 7, 8] Similarly, in Singapore, several restructured hospitals have implemented multidisciplinary heart failure clinics. The main goals of these outpatient clinics are to reduce morbidity and mortality in patients with chronic heart failure, while at the same time, providing affordable, appropriate and accessible healthcare for these patients.

1.1 Role of the pharmacist

Pharmacists play a pivotal role in improving the care of heart failure patients in an ambulatory setting. They are actively involved in:

- titrating angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and beta-blockers to their target or maximal tolerated doses.
- patient education, especially on the importance of compliance and the rationale and need for multiple drug therapy.
- imparting self-care skills like self-adjustment of diuretic doses and daily weight charting.
- screening for drug-drug interactions and for drugs that can exacerbate heart failure.
- medication reconciliation.
- monitoring for worsening signs and symptoms of heart failure.
- monitoring laboratory parameters.
- monitoring for adverse effects.
- anticoagulation management and education.
- smoking cessation.
- promoting cost-effective and rational use of medication.

1.2 Objectives of guidelines

The objectives of these guidelines are to provide an up-to-date and practical approach for the management of a patient with chronic heart failure and to assist pharmacists in the pharmacological and non-pharmacological management of chronic heart failure patients. These guidelines will support pharmacists practising in heart failure clinics in an outpatient setting, titrating mainly angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and beta-blockers to target doses after these have been first prescribed by a physician. It can also be used by other healthcare professionals concerned with the care of patients with chronic heart failure.

1.3 Scope of guidelines

There are multiple therapeutic approaches to the management of heart failure. These include pharmacological therapy, non-pharmacological therapy and surgical intervention. The focus of these guidelines will be on the pharmacological management of chronic systolic heart failure, with a brief overview of non-pharmacological management of the patient, including lifestyle modifications.

2 GRADES OF RECOMMENDATION AND LEVELS OF EVIDENCE

Grades of Recommendation

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective. The procedure or treatment should be performed/ administered.

Class IIa: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment, but the weight of evidence/opinion is in favour of usefulness/efficacy. It is reasonable to perform/ administer that treatment or procedure.

Class IIb: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment, and the usefulness/ efficacy is less well established by evidence/opinion. The procedure or treatment may be considered.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful. The procedure/ treatment should not be performed/administered.

Levels of Evidence

Level A: Sufficient evidence from multiple randomised clinical trials or meta-analyses.

Level B: Data derived from a single randomised trial, or non-randomised studies.

Level C: Only consensus opinion of experts, case studies, or standard-of-care.

3 PHARMACOLOGICAL MANAGEMENT

The aims of therapy in heart failure are to reduce morbidity and mortality, while improving the quality of life through the control of symptoms, and to slow down the progression of heart failure.

3.1 Angiotensin Converting Enzyme Inhibitors (ACE-I)

3.1.1 Considerations for initiation

- ACE-I are recommended to prevent heart failure in high risk patients who have a history of coronary artery disease, peripheral vascular disease, stroke, hypertension with associated cardiovascular risk factors or diabetes mellitus with microalbuminuria or who smoke.

  (Class IIa, Level A)

- ACE-I have been shown to improve the survival, symptoms and functional capacity as well as reduce hospitalization rates in all heart failure patients, with LVEF ≤ 40%, whether symptomatic or asymptomatic.

  (Class I, Level A)

- ACE-I should be given to all patients diagnosed with heart failure in the absence of contraindications. ACE-I should be given as the initial agent rather than an angiotensin II receptor blocker.

  (Class I, Level A)

- For patients with fluid retention, ACE-I should not be prescribed without diuretics.

  (Class I, Level B)

- Patients who cannot tolerate ACE-I due to hyperkalaemia and renal insufficiency are also likely to be intolerable to angiotensin II receptor blockers. For these patients, a combination of isosorbide dinitrate and hydralazine may be recommended, especially when the use of beta-adrenergic blockers is contraindicated.

  (Class IIb, Level C)

- ACE-I should be used with caution in patients with bilateral renal artery stenosis, aortic stenosis, very low systolic blood pressure (< 80mmHg), markedly elevated serum creatinine (> 250μmol/L) or serum potassium (> 5.5 mmol/L).[9]

- ACE-I are contraindicated in patients who have experienced life threatening adverse reactions (angioedema or anuric renal failure) while on the agent and in pregnancy.

3.1.2 Dose titration

- ACE-I should be initiated at the appropriate dose and titrated upwards at short intervals (for example, every 1 to 2 weeks) until the optimal tolerated or target dose as used in large, randomized trials is achieved.

(Class I, Level A)

- Table 1 summarizes the titration of ACE-I. Upon achieving the target dose, further increments may be necessary in the presence of persistently elevated blood pressure.

Table 1 - Recommended Angiotensin Converting Enzyme Inhibitors Dosing Guide

ACE-I	Starting dose	Increments	Target dose	Further increments	Maximum dose
Captopril	6.25mg tds	-12.5mg - 25mg -	50mg tds	- 75mg -	100mg tds
Enalapril	2.5mg bd	- 5mg - 7.5mg -	10mg bd	- 15mg -	20mg bd
Lisinopril	2.5mg - 5mg once daily	- 10mg - 15mg -	20mg once daily	- 30mg -	40mg once daily
Perindopril[#]	2mg once daily	- 4mg -	4mg once daily	- 6mg -	8mg once daily
Ramipril	1.25mg - 2.5mg daily	- 5mg -	10mg daily	-15mg -	20mg daily

[#]Use is not well established in heart failure trials

3.1.3 Considerations during titration

- Blood pressure, serum creatinine and potassium should be assessed within 2 weeks of initiation and after each dose adjustment.

- Hypotension
  - ACE-I commonly causes hypotension. If asymptomatic and systolic BP is not less than 80mmHg, a change in therapy is usually not required.
  - In cases of symptomatic hypotension, doses of vasodilators or other hypotensive agents such as nitrates or calcium-channel blockers may be reduced, unless used for angina as a compelling indication.
  - Consider staggering the time of administration of essential medication that can also contribute to lowering of blood pressure.
  - In the absence of signs or symptoms of congestion, consider reducing the diuretic dose.

- Worsening Renal Function and Hyperkalaemia
  - Some increase in serum creatinine and potassium is to be expected after initiation and dose increment of ACE-I.

- A 5% to 15% increase in serum creatinine in patients with mild heart failure[10] and 15% to 30% in patients with severe heart failure may be observed.[11]
- If serum creatinine and/or potassium do rise significantly above baseline, consider stopping concomitant nephrotoxic drugs, non-essential vasodilators and/or potassium supplements.
- If serum creatinine increases by greater than 50% above baseline, or more than 250μmol/L (3mg/dL), whichever is smaller, despite adjustment of concomitant medications, the dose of ACE-I should be halved and blood chemistry re-checked. If response remains unsatisfactory after adjustment, refer to a physician.[12]
- If serum creatinine increases by greater than 100% above baseline or beyond 300μmol/L (3.5mg/dL) or serum potassium exceeds 5.5mmol/L, patient should be referred to a physician. Discontinuation of ACE-I should be considered.[12]
- Diabetes, rather than renal impairment, appears to increase the risk of ACE-I-induced hyperkalaemia.[12]

- Cough
  - Cough is commonly associated with ACE-I treated patients (approximately 44% in Asian population[13]). It usually appears within the first month of initiation and disappears within 1 to 2 weeks of discontinuation of therapy.
  - Note that other medical conditions can also cause cough (e.g. pulmonary oedema, gastric reflux, common cold, etc.), which should be excluded when a new or worsening cough develops.
  - ACE-I-induced cough rarely requires treatment discontinuation, unless in the presence of bothersome cough. In such cases, switching to an ARB can be considered.

3.1.4 Advice to patients

- Explain that therapy with ACE-I can improve symptoms, prevent disease progression or worsening of heart failure, reduce unplanned hospitalization as well as increase survival.

- Inform that symptoms may only improve after weeks to months of initiation of therapy.

- Advise patients to report principal adverse reactions (i.e. giddiness, fainting etc. and cough), especially within the first few days of initiation or dosage increment. Inform that cough may be persistent even after 1-2 weeks of discontinuation.

- Inform that light-headedness, giddiness or postural hypotension may occur especially during first few days of initiation or up-titration phase. Patients should be advised to rise slowly from a lying, sitting or squatting position.

Algorithm for Initiation and Titration of ACE-Inhibitors in Chronic Heart Failure

Any of the following present?

- Significant renal impairment (creatinine >250µmol/L).
- Hyperkalaemia (K > 5.5mmol/L).
- Persistent symptomatic hypotension (systolic BP < 80mmHg).
- Known or suspected renal artery stenosis or aortic stenosis.
- History of adverse reactions to ACE-I (angioedema or anuric renal failure).
- Pregnancy.

No → Check with physician for ACE-I initiation

Yes

Initiate ACE-I

- Start at appropriate dose.
- Titrate upwards at short interval (e.g. every 1-2 weeks) until the optimal tolerated or target dose.
- Monitor blood pressure, serum creatinine and potassium within 2 weeks of initiation and each dose adjustment.

Hypotension

- If asymptomatic and systolic BP > 80mmHg, a change in therapy is usually not required.
- If symptomatic hypotension, doses of vasodilators or other hypotensive agents such as nitrates or calcium-channel blockers may be reduced, unless used for angina as a compelling indication.
- Consider staggering the time of administration of essential medication that can also contribute to lowering of blood pressure.
- If no signs or symptoms of congestion exist, consider reducing the diuretic dose.

Worsening Renal Function and Hyperkalaemia

- Some increase in serum Cr and K is to be expected after initiation and dose increment of ACE-I.
- If serum Cr and/or K do rise significantly above baseline, consider stopping concomitant nephrotoxic drugs, non-essential vasodilators and/or potassium supplements.
- If serum Cr increases > 50% above baseline, or > 250 µmol/L (3mg/dL), whichever is smaller, despite adjustment of concomitant medications, the dose of ACE-I should be halved and blood chemistry rechecked. If response remains unsatisfactory after adjustment, refer to physician.
- If serum Cr increases > 100% above baseline or > 300µmol/L (3.5mg/dL) or serum K > 5.5mmol/L, patient should be referred to physician. Discontinuation of ACE-I should be considered.

Cough

- Cough is commonly associated with ACE-I treated patients, usually appears within the first month of initiation and disappears within 1 to 2 weeks of discontinuation of therapy.
- Note that other medical conditions can also cause cough (e.g. pulmonary oedema, gastric reflux, common cold, etc), which should be excluded when a new or worsening cough develops.
- ACE-I-induced cough rarely requires treatment discontinuation, unless in the presence of bothersome cough. In such cases, switching to an ARB can be considered.

Adverse Effects

No Adverse Effects

Maintenance

- Aim for target dose or optimal tolerated dose.
- Explain expected benefits to patient.
- Advise patient to report principal adverse reactions (giddiness, cough).
- Even if patient feels well, therapy should not be discontinued, otherwise symptoms may recur.

Recommended Angiotensin Converting Enzyme Inhibitors Dosing Guide

ACE-I	Starting dose	Increments	Target dose	Further increments	Max dose
Captopril	6.25mg tds	- 12.5mg - 25mg -	50mg tds	- 75mg -	100mg tds
Enalapril	2.5mg bd	- 5mg - 7.5mg -	10mg bd	- 15mg -	20mg bd
Lisinopril	2.5mg - 5mg once daily	- 10mg - 15mg -	20mg once daily	- 30mg -	40mg once daily
Perindopril[#]	2mg once daily	- 4mg -	4mg once daily	- 6mg -	8mg once daily
Ramipril	1.25mg - 2.5mg daily	- 5mg -	10mg daily	-15mg -	20mg daily

[#]Use is not well established in heart failure trials

- Emphasise that therapy should not be discontinued even if patient feels well as symptoms may recur.

3.2 Angiotensin II Receptor Blockers (ARB)

3.2.1 Considerations for initiation

- ARB are useful alternatives for heart failure patients (LVEF ≤ 40%) intolerant of ACE-I due to cough. However, for patients intolerant to ACE-I due to renal insufficiency or hyperkalaemia, ARB are not recommended.

(Class I, Level A)

- ARB has been infrequently associated with angioedema. Nonetheless, in patients who develop angioedema while on ACE-I, ARB can still be used with caution.[14, 15]

- ARB may be considered as an alternative initial therapy rather than ACE-I for heart failure patients with recent myocardial infarction.[16, 17]

- The addition of ARB to existing ACE-I and β-blocker is not recommended in patients with recent myocardial infarction and left ventricular systolic dysfunction. This combination does not confer additional benefits and can contribute to higher risk of adverse events such as hypotension, hyperkalaemia and reduced renal function.[17]

(Class III, Level B)

- In patients with persistent signs and symptoms of heart failure, the addition of ARB to existing ACE-I and β-blocker may be considered. However, close monitoring of serum creatinine and potassium is necessary to prevent unwanted side effects.

(Class IIa, Level B)

3.2.2 Dose titration

- ARB should be initiated at the appropriate dose and titrated upwards at short intervals (for example, every 1 to 2 weeks) until the optimal tolerated or target dose as used in large, randomized trials is achieved.

(Class I, Level A)

- Table 2 summarizes the titration of ARB to their respective target doses.

Table 2 - Recommended Angiotensin II Receptor Blockers Dosing Guide

ARB	Starting dose	Increments	Target dose	Maximum dose
Candesartan	4mg - 8mg once daily	- 16mg – 24mg -	32mg once daily	32mg once daily
Losartan[#]	12.5mg - 25mg once daily	- 50mg – 75mg -	100mg once daily	100mg once daily
Valsartan	40mg - 80mg daily	- 160mg – 240mg -	160mg bd or 320mg once daily	320mg once daily

[#]Use is not well established in heart failure

3.2.3 Considerations during titration

- Blood pressure, serum creatinine and potassium should be assessed within 2 weeks of initiation and after each dose adjustment.

- Hypotension
  - ARB commonly causes hypotension. If asymptomatic and systolic BP is not less than 80mmHg, a change in therapy is usually not required.
  - In cases of symptomatic hypotension, doses of vasodilators or other hypotensive agents such as nitrates or calcium-channel blockers may be reduced, unless used for angina as a compelling indication.
  - Consider staggering the time of administration of essential medication that can also contribute to lowering of blood pressure.
  - In the absence of signs or symptoms of congestion, consider reducing the diuretic dose.

- Worsening Renal Function and Hyperkalaemia
  - Some increase in serum creatinine and potassium is to be expected after initiation and dose increment of ARB.
  - If serum creatinine and/or potassium do rise significantly above baseline, consider stopping concomitant nephrotoxic drugs, non-essential vasodilators and/or potassium supplements.
  - If serum creatinine increases by greater than 50% above baseline, or more than 250μmol/L (3mg/dL), whichever is smaller, despite adjustment of concomitant medications, the dose of ARB should be halved and blood chemistry re-checked. If response remains unsatisfactory after adjustment, refer to a physician.[12]
  - If serum creatinine increases by greater than 100% above baseline or beyond 300μmol/L (3.5mg/dL) or serum potassium exceeds 5.5mmol/L, patient should be referred to a physician. Discontinuation of ARB should be considered.[12]

Algorithm for Initiation and Titration of ARB in Chronic Heart Failure

Any of the following present?

- Significant renal impairment (creatinine >250μmol/L).
- Hyperkalaemia (K > 5.5mmol/L).
- Persistent symptomatic hypotension (systolic BP < 80mmHg).
- Known or suspected renal artery stenosis or aortic stenosis.
- History of adverse reactions to ACE-I (angioedema or anuric renal failure). Not an absolute contraindication for initiating ARB but use with caution.
- Pregnancy.

No → Check with physician for ARB initiation

Yes ↓

Initiate ARB

- Start at appropriate dose.
- Titrate upwards at short interval (e.g. every 1-2 weeks) until the optimal tolerated or target dose.
- Monitor blood pressure, serum creatinine and potassium within 2 weeks of initiation and each dose adjustment.

Hypotension

- If asymptomatic and systolic BP > 80mmHg, a change in therapy is usually not required.
- If symptomatic hypotension, doses of vasodilators or other hypotensive agents such as nitrates or calcium-channel blockers may be reduced, unless used for angina as a compelling indication.
- Consider staggering the time of administration of essential medication that can also contribute to lowering of blood pressure.
- If no signs or symptoms of congestion exist, consider reducing the diuretic dose.

Worsening Renal Function and Hyperkalaemia

- Some increase in serum Cr and K is to be expected after initiation and dose increment of ARB.
- If serum Cr and/or K do rise significantly above baseline, consider stopping concomitant nephrotoxic drugs, non-essential vasodilators and/or potassium supplements.
- If serum Cr increases > 50% above baseline, or > 250 μmol/L (3mg/dL), whichever is smaller, despite adjustment of concomitant medications, the dose of ARB should be halved and blood chemistry rechecked. If response remains unsatisfactory after adjustment, refer to physician.
- If serum Cr increases > 100% above baseline or > 300μmol/L (3.5mg/dL) or serum K > 5.5mmol/L, patient should be referred to physician. Discontinuation of ARB should be considered.

Cough

- Cough is less commonly associated with ARB treated patients.

Angioedema

- Angioedema is occasionally associated with ARB, especially in patients with prior experience while taking ACE-I.
- The incidence of angioedema may be delayed by more than 1 year after initiation of ARB. Hence, careful monitoring is necessary, especially in patients who demonstrated history of angioedema while receiving ACE-I. In the event of airways compromise in the mouth or throat region, immediate medical attention is required.

Adverse Effects ↓

No Adverse Effects ↓

Maintenance

- Aim for target dose or optimal tolerated dose.
- Explain expected benefits to patient.
- Advise patient to report principal adverse reactions (giddiness, cough).
- Even if patient feels well, therapy should not be discontinued, otherwise symptoms may recur.

Recommended Angiotensin II Receptor Blockers dosing guide

ARB	Starting dose	Increments	Target dose	Maximum dose
Candesartan	4mg - 8mg once daily	- 16mg - 24mg -	32mg once daily	32mg once daily
Losartan#	12.5mg - 25mg once daily	- 50mg - 75mg -	100mg once daily	100mg once daily
Valsartan	40mg - 80mg daily	- 160mg - 240mg -	160mg bd or 320mg once daily	320mg once daily

#Use is not well established in heart failure

- Cough
  - Cough is less commonly associated with ARB as compared to ACE-I.[18]

- Angioedema
  - Angioedema is occasionally associated with ARB, especially in patients with prior experience while taking ACE-I.
  - The incidence of angioedema may be delayed by more than 1 year after initiation of ARB.[19] Hence, careful monitoring is necessary, especially in patients who demonstrated history of angioedema while receiving ACE-I. In the event of airways compromise in the mouth or throat region, immediate medical attention is required.

3.2.4 Advice to patients

- Explain that therapy with ARB can improve symptoms, prevent disease progression or worsening of heart failure, reduce unplanned hospitalization as well as increase survival.

- Inform that symptoms may only improve after weeks to months of initiation of therapy.

- Advise patients to report principal adverse reactions (i.e. giddiness, fainting etc. and cough), especially within the first few days of initiation or dosage increment. Inform that cough may be persistent even after 1-2 weeks of discontinuation.

- Inform that light-headedness, giddiness or postural hypotension may occur especially during first few days of initiation or up-titration phase. Patients should be advised to rise slowly from a lying, sitting or squatting position.

- Emphasise that therapy should not be discontinued even if patient feels well as symptoms may recur.

3.3 Beta-adrenergic Blockers (β-blocker)

3.3.1 Considerations for initiation

- β-blockers can reduce the risk of death, the combined risk of death and hospitalization, improve functional status and lead to improved cardiac function and lessen symptoms of heart failure.

(Class I, Level A)

- β-blockers (bisoprolol, carvedilol or long-acting metoprolol) should be initiated in patients with stable heart failure due to left ventricular systolic dysfunction (LVEF ≤ 40%) with or without ACE-I therapy.[20, 21]

(Class I, Level B)

- β-blockers are recommended in patients with heart failure and preserved LVEF who have prior or recent episode of myocardial infarction.

(Class I, Level A)

- β-blockers should not be prescribed without diuretics in patients with a current or recent history of fluid retention. Diuretics are needed to maintain fluid status and prevent the development of fluid retention that may follow the initiation of β-blockade.

- β-blockers should be used with caution in the presence of persistent symptomatic hypotension (systolic BP < 80mmHg), bradycardia (heart rate < 60 beats per minute), reactive airway disease, second or third degree heart block, diabetes especially with recurrent hypoglycaemia and ischemic limb disease especially if severely symptomatic.

3.3.2 Dose titration

- β-blocker therapy for heart failure should be introduced in a "start low, go slow" manner. It is recommended to increase the dose gradually at 2-week intervals with re-assessment of blood pressure and heart rate.

(Class 1, Level B)

- Table 3 summarizes the titration of β-blockers to their respective target doses.

Table 3 - Recommended Beta-adrenergic Blockers Dosing Guide

β-blocker	Starting dose	Increments	Target dose
Bisoprolol	1.25mg once daily	- 2.5mg – 3.75mg – 5mg – 7.5mg -	10mg once daily
Carvedilol	3.125mg bd	- 6.25mg – 12.5mg – 25mg -	25mg – 50mg bd*
Metoprolol Succinate	12.5mg - 25mg once daily	- 50mg – 100mg -	200mg once daily

* For patients weighing more than 85kg, up to 50mg bd can be used

3.3.3 Considerations during titration

- Worsening Signs and Symptoms of Heart Failure
  - As a result of the β-blockade, patients may experience a transient worsening of heart failure, evident by signs and symptoms like weight gain or fluid retention.

- In the presence of increasing congestion, consider doubling the dose of the diuretic and/or reducing the dose of the β-blocker (if increasing the diuretic is ineffective).
- In the presence of significant fatigue, consider reducing the dose of the β-blocker.
- For any dosage adjustment to the β-blocker, a review is recommended in 1 to 2 weeks' time.
- During chronic maintenance therapy, continuation of the β-blocker is recommended in most patients experiencing a symptomatic exacerbation of heart failure. However, a temporary dose reduction may be considered. Abrupt discontinuation should be avoided.[9, 16]
- If serious deterioration occurs, consider reducing the dose of or withdrawing the β-blocker (rarely necessary) and refer to a physician.

• Bradycardia
  - In the presence of a heart rate of less than 50 beats per minute and/or worsening symptoms, refer to a physician.
  - Withdrawal of negative chronotropes, e.g. digoxin, in favour of β-blocker may be considered, unless indicated for control of atrial fibrillation.

• Hypotension
  - β-blockers commonly cause hypotension. If asymptomatic and systolic BP is not less than 80mmHg, a change in therapy is usually not required.
  - In cases of symptomatic hypotension, doses of vasodilators or other hypotensive agents such as nitrates or calcium-channel blockers may be reduced, unless used for angina as a compelling indication.
  - Consider staggering the time of administration of essential medication that can also contribute to lowering of blood pressure.
  - In the absence of signs or symptoms of congestion, consider reducing the diuretic dose.

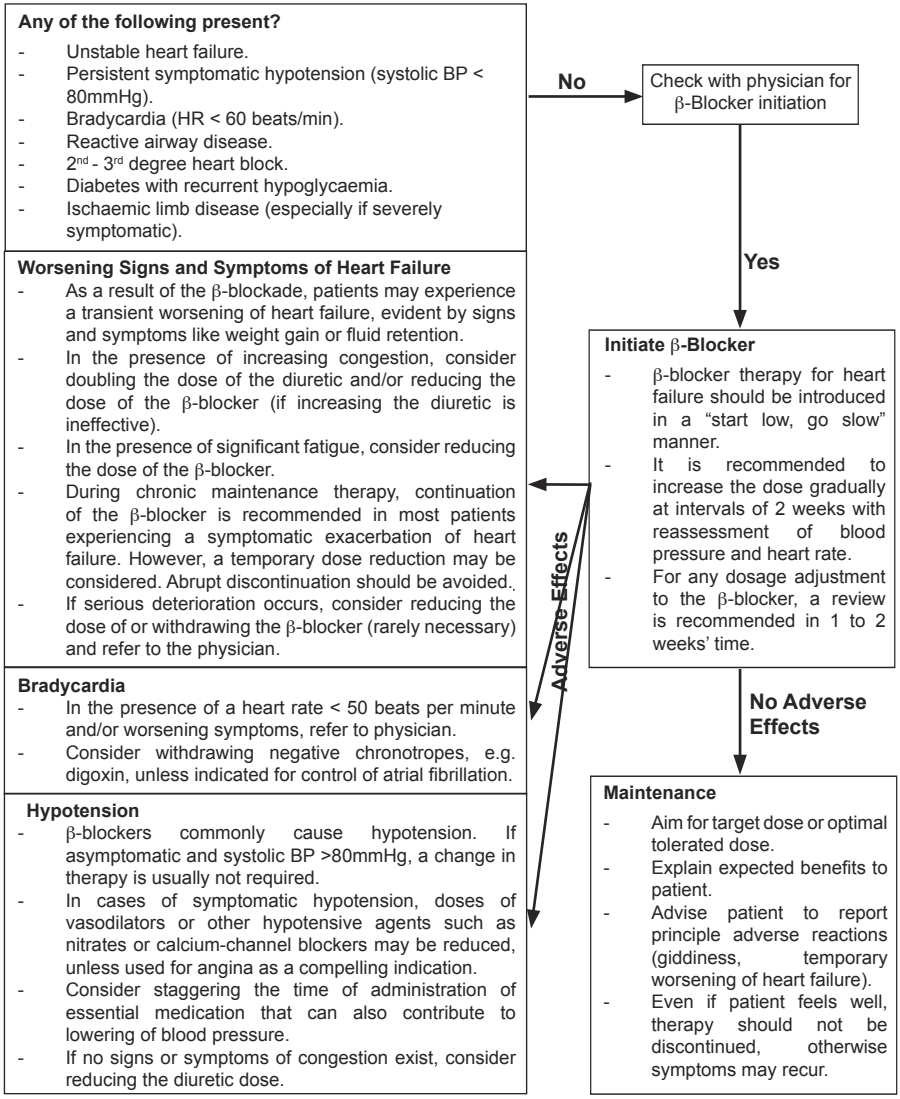
3.3.4 Advice to patients

- Explain that therapy with β-blocker can improve heart failure, prevent worsening of heart failure and increase survival.

- Inform that clinical responses are generally delayed and may require 8 to 12 weeks or longer to become apparent.[22, 23]

- As temporary symptomatic deterioration may occur during initiation of therapy or up-titration phase, patients should be advised to monitor for and report symptoms of deterioration (e.g. fatigue, dyspnoea, oedema or other signs and symptoms of fluid retention).

Algorithm for Initiation and Titration of Beta-Blockers in Chronic Heart Failure



Recommended Beta-adrenergic Blockers Dosing Guide

β-blocker	Initial dose	Increments	Target dose
Bisoprolol	1.25mg once daily	- 2.5mg - 3.75mg - 5mg - 7.5mg -	10mg once daily
Carvedilol	3.125mg bd	- 6.25mg - 12.5mg - 25mg -	25mg - 50mg bd*
Metoprolol Succinate	12.5mg - 25mg once daily	- 50mg - 100mg -	200mg once daily

* For patients weighing more than 85kg, up to 50mg bd can be used

- Inform that light-headedness, giddiness or postural hypotension may occur especially during first few days of initiation or up-titration phase. Patients should be advised to rise slowly from a lying, sitting or squatting position.

- Highlight that abrupt discontinuation of β-blockade therapy is not recommended as it may lead to worsening of heart failure symptoms.

- Emphasise that therapy should not be discontinued even if patient feels well as symptoms may recur.

3.4 Aldosterone Antagonists (AA)

3.4.1 Considerations for initiation

- The addition of low dose AA should be considered in patients with moderately severe or severe heart failure symptoms and recent decompensation, or with LV dysfunction early after myocardial infarction. [24, 25]

(Class I, Level B)

- Low dose spironolactone should be considered for patients on standard therapy who have severe heart failure (NYHA class III-IV). [24]

(Class I, Level B)

- In patients with LVEF ≤40% and clinical evidence of heart failure or diabetes post myocardial infarction, eplerenone has been shown to reduce mortality and cardiovascular morbidity.[25]

(Class I, Level B)

- AA should not be used in patients with creatinine > 220μmol/L (> 2.5mg/dL), and/or potassium > 5mmol/L. Under circumstances where monitoring for hyperkalaemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of using AA.[24, 25]

(Class I, Level B)

- In elderly patients or patients with low muscle mass in whom serum creatinine does not accurately reflect glomerular filtration rate, ensure that CrCl exceeds 30ml/min before use of AA.

3.4.2 Dose recommendation

- An initial dose of spironolactone 12.5mg once daily or eplerenone 25mg once daily is recommended, after which the dose may be increased to spironolactone 25mg or eplerenone 50mg if appropriate.

- In the absence of persistent hypokalaemia (< 4mmo/L), supplemental potassium is not recommended in patients taking AA.[24, 26, 27, 28]

(Class I, Level A)

3.4.3 Monitoring parameters

- Serum potassium concentration should be monitored within 2 weeks following initiation or dosage change of an AA.

- Impaired renal function is a risk factor for hyperkalaemia during treatment with AA. The risk of hyperkalaemia increases progressively when serum creatinine exceeds 140μmol/L (1.6mg/dL).

- If potassium level rises above 5.5mmol/L or creatinine rises above 220μmol/L (2.5 mg/dL), reduce dose of AA.

- If potassium level rises to above 6.0mmol/L or creatinine above 310μmol/L (3.5 mg/dL) stop AA and refer to a physician.

- Patients chronically requiring high doses of diuretics without potassium replacement should be evaluated closely, because potassium handling may be impaired.

- Potassium supplementation should generally be stopped after the initiation of AA and patients should be counselled to avoid food high in potassium. However, patients who have required large amounts of potassium supplementation may need to continue receiving supplementation, albeit at a lower dose, particularly when previous episodes of hypokalaemia have been associated with ventricular arrhythmias.

3.4.4 Advice to patients

- Indication - To suppress hormone (aldosterone) that affects the heart. Treatment is given to improve symptoms, prevent worsening of heart failure and to increase survival. Symptom improvement occurs within a few weeks to months of starting treatment.

- Side effects - weight gain, breast tenderness (especially in males).

- Potassium supplementation is generally stopped after the initiation of AA. Patients should be counselled to moderate consumption of foods high in potassium and salt substitutes.

- Inform that prolonged diarrhoea or other causes of dehydration warrants medical attention.

3.5 Vasodilators (Hydralazine plus Isosorbide Dinitrate)

3.5.1 Considerations for initiation

- Patients with contraindications or intolerance (e.g. renal insufficiency) to

more effective agents (ACE-I and ARB) can be considered for treatment with the combination of hydralazine and isosorbide dinitrate.[29, 30, 31, 32]

(Class IIb, Level C)

- The addition of a combination of hydralazine and isosorbide dinitrate is reasonable for patients with reduced LVEF who are already taking an ACE-I and β-blocker for symptomatic heart failure and who have persistent symptoms.

(Class IIa, Level B)

3.5.2 Dose recommendation

- Hydralazine may be initiated at 10mg tds-qds, stepping up to 25mg tds-qds and thereafter at 25mg increments per dose (e.g. 25mg tds-qds – 50mg tds-qds etc.) up to maximum of 100mg qds.

- Isosorbide dinitrate may be initiated at 5-10mg tds-qds and stepped up as tolerated, up to 120-160mg per day.

- Can consider switching to isosorbide mononitrate if patient is tolerating isosorbide dinitrate.

3.5.3 Monitoring parameters

- Blood pressure: If systolic BP < 80mmHg and/or patient has signs of orthostasis with vasodilator therapy, do not begin or increase dose.

- Compliance may be an issue.[29, 30]

3.5.4 Advice to patients

- Indication - Relax blood vessels, increase oxygen supply to the heart.

- Precautions - Rise slowly from sitting or lying position or when changing posture to allow time for body to accommodate change in blood pressure.

- Side effects:
  - Isosorbide dinitrate: headaches, flushing, dizziness.
  - Hydralazine: palpitations, flushing, swelling of feet/lower legs, gastrointestinal side effects may occur.

- Dealing with side effects - Flushing, headache and giddiness are usually transient and are more significant at initiation or during up titration of dose. Side effects will usually diminish with continued use. However, patients should inform their healthcare provider if symptoms persist or are unbearable.

3.6 Diuretics

3.6.1 Considerations for initiation

- Diuretics are essential for symptomatic treatment when any fluid overload is present and/or manifests as pulmonary congestion or peripheral oedema. The use of diuretics results in rapid improvement of dyspnoea and increased exercise tolerance.[33, 34]

(Class I, Level A)

- There are no randomised controlled trials assessing the effects on symptoms or survival with the use of diuretics alone. When used, diuretics should always be used in addition to standard therapy.

(Class I, Level C)

- The use of inappropriately low doses of diuretics will result in fluid retention, which can diminish the response to ACE-I and increase the risk of treatment with β-blocker.[35]

- Conversely, the use of inappropriately high doses of diuretics will lead to volume contraction, which can increase the risk of hypotension[35, 36] and the risk of renal insufficiency with ACE-I and ARB.[37]

- Loop diuretics, rather than thiazide-type diuretics, are typically necessary to restore normal volume status in patients with heart failure.

- If CrCl < 30ml/min, thiazide-type diuretics (except metolazone) are ineffective when used alone. Use only when prescribed with loop diuretics for synergism. Metolazone will generally be more potent and much longer-acting in this setting.

(Class IIa, Level C)

- Addition of hydrochlorothiazide or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high-dose loop diuretic therapy.

- Chronic combined use of multiple diuretics can give rise to electrolyte shifts and volume depletion, hence volume status and electrolytes must be monitored closely.

(Class IIa, Level C)

3.6.2 Dose recommendation

- Diuretics may be initiated and titrated according to fluid status and renal function.

- Table 4 shows the diuretics that are recommended for use in the treatment of fluid retention in heart failure.

Table 4 - Diuretics Recommended for Use in the Treatment of Fluid Retention in Heart Failure

Drug	Usual Oral Daily Dose
Loop diuretics Bumetanide Frusemide	0.5mg - 2mg once to twice daily 20mg - 80mg once to twice daily
Thiazide diuretics (for sequential blockade) Hydrochlorothiazide Metolazone	12.5mg - 25mg once to twice daily 2.5mg - 5mg once daily

3.6.3 Monitoring parameters

- Record the patient's body weight and clinical symptoms of fluid retention at each visit.

- If there is an insufficient response to the diuretic, consider
  - Increasing dose and/or frequency of diuretic
  - Combining loop diuretic and a thiazide-type diuretic (If CrCl<30ml/min, consider adding metolazone).

- Diuretic refractoriness may represent patient non-compliance, a direct effect of diuretic use on the kidney, progression of underlying cardiac dysfunction, cardio-renal syndrome or failure to restrict salt and water intake.

- Decreasing or discontinuing diuretics may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful monitoring for recurrent fluid retention.

  (Class IIa, Level C)

- The principal adverse effects of diuretics include electrolyte and fluid depletion, as well as hypotension and azotemia.

- Careful observation for the development of side effects is recommended in patients treated with diuretics especially when used at high doses and in combination, including
  - Electrolyte abnormalities
  - Renal dysfunction
  - Symptomatic hypotension
  - Ototoxicity (with higher doses)

  (Class IIa, Level B)

- Diuretics can cause the depletion of important cations (potassium and magnesium), which can predispose patients to serious cardiac arrhythmias, particularly in the presence of digoxin therapy.[38]

- Hypokalaemia may be corrected with the use of potassium supplements. When ACE-I, ARB or AA is concurrently used, long-term oral potassium supplementation may not be required.

- Worsening renal function is common with excessive diuresis, especially when patients are receiving ACE-I or ARB. Reduction in diuretic dose and restoration of euvolaemia will likely return renal function to baseline in almost all cases unless hypovolaemia has been prolonged. In the presence of renal impairment, consider discontinuing nephrotoxic drugs.

- Hypotension may be a sign of volume depletion. Symptoms may include fatigue and shortness of breath rather than the more predictable symptoms of dizziness.

3.6.4 Advice to patients

- Indication - To remove excess fluid in the body by increasing urine flow.

- Side effects - Nausea, muscle cramps.

- Diuretic doses may frequently need adjustment according to body weight, signs and symptoms of fluid retention.

- Patients are advised to weigh themselves on a regular basis (preferably as part of a regular daily routine, for instance after morning toilet). In case of a sudden unexpected weight gain of > 2 kg in 3 days and/or > 3 kg over 1 week, to alert a healthcare provider or adjust their diuretic dose accordingly (e.g. increase the dose if a sustained weight gain is noted).

- Patients should be taught to recognise other signs and symptoms of fluid retention (e.g. shortness of breath, lower limb swelling).

(Class IIa, Level C)

- Selected patients may be educated to adjust daily dose of diuretic in response to weight gain and symptoms of fluid overload.

(Class IIa, Level C)

- In situations that may predispose to dehydration, e.g. prolonged diarrhoea and profuse sweating in hot weather, patients may be instructed to reduce the dose of diuretics or increase fluid intake.

3.7 Digoxin

3.7.1 Considerations for initiation

- Digoxin can be considered for patients with symptomatic heart failure (NYHA class II-IV) who are on standard therapy.[39, 40, 41, 42, 43]

(Class I, Level A)

- Digoxin may reduce hospitalisation in heart failure patients in sinus rhythm, especially in worsening heart failure caused by left ventricular dysfunction treated with ACE-I, β-blocker, diuretics and, in severe heart failure, spironolactone.[44]

(Class IIa, Level A)

- Treatment with digoxin can improve symptoms, quality of life, and exercise tolerance in patients with mild to moderate heart failure. [45, 46, 47, 48, 49, 50]

- If patient is currently on digoxin but not an ACE-I or β-blocker, treatment with digoxin should not be withdrawn. Instead, appropriate therapy with ACE-I and/or β-blocker should be instituted.

- Digoxin is indicated in atrial fibrillation and any degree of symptomatic heart failure, whether or not left ventricular dysfunction is the cause.[51]

(Class I, Level B)

- Digoxin is not indicated as primary therapy for the stabilization of patients with an acute exacerbation of heart failure symptoms, including fluid retention or hypotension.

- Digoxin should be used cautiously in patients taking other drugs that can depress sinus or AV nodal function or affect digoxin levels (e.g. amiodarone or β-blocker), even though such patients usually tolerate digoxin without difficulty.

- Contraindications to the use of cardiac glycosides include Bradycardia, 2nd and 3rd AV block, sick sinus syndrome, carotid sinus syndrome, Wolff-Parkinson-White Syndrome, hypertrophic obstructive cardiomyopathy, hypokalaemia and hyperkalaemia.

3.7.2 Dose recommendation

- Digoxin may be initiated and maintained at a dose of 62.5mcg - 125mcg daily. Low doses (62.5mcg daily or every other day) may be used initially if the patient is more than 70 years old, has impaired renal function or has a low lean body mass.
- Higher doses (>250mcg daily) are rarely used or needed in the management of patients with heart failure in the absence of atrial fibrillation.

- Loading doses of digoxin to initiate therapy in patients with heart failure is not recommended.

- In the majority of patients, there is no need to up-titrate the dosage of digoxin according to serum digoxin concentration.[35]

(Class IIb, Level A)

3.7.3 Monitoring parameters

- Digoxin at a serum concentration of between 0.5ng/ml and 0.9ng/ml has been shown to reduce mortality and hospitalization in all heart failure patients.[52]

- However, routine monitoring of serum digoxin level is often not required. Consider obtaining digoxin level if:
  - Renal function worsens.
  - Patient exhibits signs of toxicity (confusion, nausea, visual disturbances, anorexia, arrhythmia).
  - There is high level of suspicion of patient non-compliance.

- Overt digitalis toxicity is commonly associated with serum digoxin levels >3ng/ml. However, toxicity may occur with lower digoxin levels, especially if hypokalaemia, hypomagnesaemia or hypothyroidism coexists.[53, 54]

- The dose of digoxin may need to be reduced when drugs that increase serum digoxin concentration are added (e.g. amiodarone).

- Digoxin doses may require reduction while optimising beta-blocker therapy, because of the risk of bradycardia.

3.7.4 Advice to patients

- Indication – Improve the strength and pumping action of the heart resulting in better blood circulation.

- Side effects of digoxin include loss of appetite, nausea, vomiting and diarrhoea initially.

- Toxicity of digoxin include: Gastrointestinal symptoms (e.g. nausea and vomiting, anorexia, diarrhoea), cardiovascular symptoms (e.g. irregular heart beat, slow heart rate), neurological symptoms (e.g. disorientation, confusion) and visual disturbances (e.g. blurred vision, halos around bright objects, yellow discolouration). Inform that these symptoms warrant immediate medical attention.

3.8 Antiarrhythmics

- In patients with atrial fibrillation and heart failure, heart rate can be controlled with the use of β-blockers or digoxin, either alone or in combination.[55]

- The combination of digoxin and β-blocker appears superior to either agent alone in patients with atrial fibrillation.[56]

(Class IIa, Level B)

- Amiodarone restores and maintains sinus rhythm in patients with heart failure even in the presence of enlarged left atria, and improves the success of cardioversion. [57, 58] It has been associated with overall neutral effects on survival when given to patients with low EF and heart failure. [59, 60, 61, 62] Despite its numerous side effects, it remains the agent most likely to be safe and effective when antiarrhythmic therapy is necessary to prevent recurrent atrial fibrillation or symptomatic ventricular arrhythmias.[57]

(Class IIa, Level B)

- Patients with atrial fibrillation or ventricular arrhythmias should not be treated with class I antiarrhythmic drugs such as procainamide, quinidine, propafenone and flecainide because of the concern of proarrhythmia and increased mortality. [63, 64, 65]

- Sotalol has also been associated with proarrhythmia and increased mortality when used in patients with recent myocardial infarction and reduced EF.[66]

- Calcium channel blockers, particularly verapamil and diltiazem, can depress myocardial function and increase the risk of worsening heart failure and thus should be avoided. [67, 68]

3.9 Calcium Channel Blockers (CCB)

- CCB of the non-dihydropyridines class (diltiazem and verapamil) and the short-acting dihydropyridines (e.g. nifedipine) can depress myocardial function and increase the risk of heart failure decompensation and thus should be avoided.

(Class III, Level A)

- Negative inotropic effect of non-dihydropyridines may worsen symptoms, while the vasodilatory effect of short-acting dihydropyridines may further stimulate the release of sympathetic hormones.

- Two vasoselective dihydropyridines, amlodipine and felodipine, were studied and may be permissible in heart failure patients as they have not shown to cause harm.[69, 70]

(Class IIb, Level C)

- Amlodipine and felodipine may be used in the presence of inadequate control of
  - Blood pressure with other recommended agents
  - Anginal symptoms with recommended beta-blockers

3.10 Antithrombotics

- Dilated cardiac chambers in heart failure result in poor contractility, low cardiac output, stasis and flow abnormalities, and predispose such patients to higher risks of thromboembolism.[71] The incidence of thromboembolic events in heart failure patients is approximately 2%,[72] but the incidence of occult thromboembolism may be higher. Routine use of antithrombotic therapy (aspirin, warfarin, low molecular weight heparin) in patients with heart failure is controversial.

3.10.1 Considerations for initiation

- Aspirin should be used in patients with compelling indications.

  (Class I, Level B)

- Based on current data, the use of aspirin for the sole indication of left ventricular systolic dysfunction is not recommended.[73]

- Due to conflicting evidence, the use of warfarin for the sole indication of left ventricular systolic dysfunction in heart failure may not be recommended.[74, 75, 76]

- In heart failure patients with atrial fibrillation, treatment with warfarin is indicated. Suggested therapeutic INR range is 2 - 3.

  (Class I, Level A)

4.1 Hypertension, hyperlipidaemia and diabetes mellitus in heart failure

- Progression of heart failure is frequently associated with decreases in blood pressure (due to deterioration of cardiac performance) and decreases in serum lipids (due to development of cardiac cachexia). [77]

- Benefits of drugs used to lower blood pressure or blood lipids may be seen only during prolonged periods of treatment, i.e. those that exceed the expected life span of many patients with heart failure. [77, 78, 79, 80] Thus, little is known about the benefits of treating hypertension, hypercholesterolaemia, or diabetes mellitus in patients with established reduced LVEF and symptoms of heart failure. Nevertheless, it is prudent to manage hypertension, hyperlipidaemia and diabetes mellitus in patients with heart failure as if the patients did not have heart failure.

  (Class IIa, Level B)

- Control of blood pressure may be especially important in patients with heart failure and preserved LVEF, whose symptoms may respond particularly well to blood pressure lowering treatment.[81, 82]

  (Class IIa, Level B)

- Heart failure can complicate the management of diabetes mellitus. It is associated with resistance to the actions of insulin,[83, 84] and the resulting hyperinsulinemia may promote both cardiac and vascular hypertrophy.[85, 86, 87]

  (Class IIa, Level B)

- These mechanisms may compound the deleterious effects of accelerated atherosclerosis and altered energy metabolism on cardiac function and may help to explain why diabetic patients with heart failure have a worse prognosis than their non-diabetic counterparts.[88]

4.2 Medication use for hypertension and diabetes mellitus in heart failure

- Drugs that can both control blood pressure and treat heart failure should be preferred in patients with both conditions; this includes the use of diuretics, ACE-I, and β-blockers.

  (Class IIa, Level B)

- The use of calcium channel blockers in the treatment of hypertension in heart failure is mentioned in section 3.9.

- Potent direct-acting vasodilators such as minoxidil should be avoided, because of their sodium-retaining effects.

  (Class I, Level C)

- ACE-I and β-blockers prevent the progression of heart failure in diabetic and non-diabetic patients.[89, 90, 91] β-blockers should not be avoided in diabetic patients despite fears that these drugs may mask symptoms of hypoglycemia produced by anti-diabetic therapy or may exacerbate glucose tolerance or insulin resistance.

(Class I, Level B)

- Thiazolidinediones (TZD) in heart failure has been associated with weight gain, peripheral oedema and symptomatic heart failure in patients with underlying risk factors or known cardiovascular disease. The risk of developing oedema with TZD is dose-related and is higher for those who are on concomitant insulin. The incidence is low in patients with NYHA functional class I to II symptoms, and TZD may be administered safely with careful monitoring for fluid retention.

- Initiation of TZDs is not recommended in patients with NYHA functional class III to IV symptoms of heart failure.[92, 93]

(Class I, Level A)

- Metformin may be used with appropriate monitoring and should be avoided in severe heart failure and concomitant renal dysfunction.

(Class IIb, Level C)

4.3 Management of concomitant hypertension, hyperlipidaemia and/or diabetes mellitus in heart failure [94]

- Lifestyle and dietary modification should be advocated, pharmacological management when required (refer to Appendix for details).

4.4 Management of anaemia in heart failure

- Anaemia is an independent factor of mortality[95] and increases hospitalization, regardless of systolic function.[96, 97, 98]

- The routine need to improve erythropoiesis with erythropoietin and intravenous iron has not been established, due to lack of studies and current conflicting results.[9, 99, 100]

(Class IIb, Level C)

- Usual practice of management of anaemia should be observed. There are currently no standard guidelines for the treatment of anaemia in heart failure patients.

5 NON-PHARMACOLOGICAL MANAGEMENT IN HEART FAILURE

Non-pharmacologic management of patients with heart failure significantly impacts the patient's stability, quality of life, functional capability and mortality.

(Class IIa, Level B)

5.1 Sodium and potassium restriction

- Moderate sodium restriction and daily measurement of weight may permit effective use of lower and safer doses of diuretic drugs. This is important because loop diuretics increase plasma renin activity, leading to adverse outcomes through neurohormonal stimulation.[101]

(Class IIa, Level B)

- Potassium-rich foods, especially salt substitutes, should be consumed with caution in patients prone to hyperkalaemia, especially while they are on agents that inhibit the renin-angiotensin-aldosterone cascade.

- Dietary recommendations should be provided to all heart failure patients with co-morbidities like diabetes mellitus, hyperlipidaemia, hypertension and renal impairment.

(Class IIa, Level B)

5.2 Fluid restriction

- Fluid restriction should be considered for all patients demonstrating fluid retention that is difficult to control despite diuretic use and sodium restriction.[102, 103]

(Class IIa, Level B)

5.3 Weight management

- Obesity contributes to the development of additional heart failure risk factors, including hypertension, LV hypertrophy and diastolic filling abnormalities. Obesity is linked with insulin resistance and glucose intolerance, hyperaldosteronism, salt sensitivity and plasma volume expansion, creating both pressure and volume overload stressors with increased systemic vascular resistance. Excessive adipose tissue increases cardiac output requirements. Cardiomyopathy with heart failure is the leading cause of death in obesity.

- Weight loss and sodium restriction are effective to improve symptoms and prognosis.[104]

(Class IIa, Level C)

- Caloric supplementation, by ensuring high-energy diets and/or altering size and frequency of meals, may be warranted in patients with advanced heart failure and unintentional weight loss or muscle wasting (cardiac cachexia).[105]

(Class I, Level B)

- Sleep apnoea is commonly seen in obesity, and mimics symptoms of pulmonary congestion and should be ruled out. Further, in patients with concomitant heart failure, it is an adverse prognostic indicator. Efficacy of therapeutic intervention is controversial.[106, 107]

5.4 Exercise and exercise training

- A reduction in physical activity leads to a state of physical deconditioning that contributes to the symptoms and exercise intolerance of patients with chronic heart failure.[108, 109]

(Class IIa, Level B)

- Although most patients should not participate in heavy labour or exhaustive sports, physical activity should be encouraged (except during periods of acute exacerbation of heart failure or in patients with suspected myocarditis).[109, 110, 111]

(Class IIa, Level B)

- Observations suggest that exercise training may have a favourable effect on the natural history of heart failure,[112, 113, 114] lessening symptoms, increasing exercise capacity, and improving the quality of life of patients with chronic heart failure.[114, 115, 116, 117, 118, 119, 120, 121, 122, 123] Improvement was comparable to that achieved with pharmacologic interventions,[124] and was in addition to the benefits of ACE-I and β-blockers.[112, 116]

- Only one study has evaluated the long term effect of physical conditioning in patients with heart failure.[123] Exercise training may be considered for all stable outpatients with chronic heart failure who are able to participate in the protocols needed to produce physical conditioning, and should be used in conjunction with drug therapy.

(Class IIa, Level C)

5.5 Alcohol consumption

- Excessive alcohol consumption may lead to adverse outcomes such as hypertriglyceridaemia, hypertension, liver damage, and increased risk of breast cancer. Should alcohol be consumed, quantities should be limited since moderate alcohol consumption has been associated with reduced cardiovascular outcomes.[125]

- Men should be restricted to 1-2 drinks per day and women 1 drink per day, and these drinks should be consumed with meals.

(Class I, Level B)

- A standard drink is equal to 13.7 grams of pure alcohol or the following drink equivalents[126]
  - 12-ounces (360ml) of beer
  - 8-ounces (240ml) of malt liquor
  - 4-ounces (120ml) of wine
  - 1.5-ounces (45ml) or a “shot” of 80-proof distilled spirits or liquor (gin, rum, vodka, whiskey, etc)
  - 1-ounce (30ml) of 100-proof distilled spirits

- Patients with alcoholic cardiomyopathy should abstain from alcohol consumption.[127, 128, 129]

(Class I, Level A)

5.6 Smoking Cessation

- Smoking cessation in individuals with heart failure potentially confers greater benefit than it does in the general population.[130] Nicotine, a vasoconstrictor, can worsen haemodynamics and antagonize vasodilation effects of the medications used in heart failure.

- As such, all tobacco products should be avoided and exposure to second hand smoke should be minimized.[131, 132, 133]

(Class I, Level C)

- While it is important that efforts be made to prevent weight gain after smoking cessation, the benefits of smoking cessation outweigh any potential body weight gained.

5.7 Immunization

- Pulmonary congestion can increase the risk of lung infections. Pneumococcal vaccination and annual influenza vaccination are recommended in all patients with heart failure in the absence of known contraindications.[134, 135]

(Class IIa, Level B)

- Patients should be counselled to seek early evaluation for potentially serious infections.

6 MEDICATION/SUPPLEMENTS WHICH SHOULD BE AVOIDED OR USED WITH CAUTION IN HEART FAILURE

A complete medication history, including vitamins and supplements should be obtained from all patients at every visit. Pharmacists have an important role of screening for any drug-drug and/or drug-herb interactions, and drug/herb-disease interactions. Patients should be counselled on drugs and supplements that are to be avoided where possible, especially when consuming without the knowledge of their primary-care physician.

The following table may be used as a guide:

Table 5 - Medication/ Herbs which should be Avoided or Used with Caution in Heart Failure[9, 136]

Drug/Herb	Comments	Suggested Action
NSAIDs/COX-2 inhibitors.	Exacerbate oedema and renal impairment by inhibiting prostaglandins and hence compromising renal blood flow. COX-2 inhibitors may increase cardiovascular events.[137]	Avoid unless compelling indication. Limit use to lowest effective dose for the shortest duration.
Glucocorticoids, androgens, oestrogens.	Exacerbate oedema by increasing re-absorption of sodium.	Use with caution.
Calcium channel blockers e.g. non-dihydropyridines (verapamil, diltiazem), short-acting dihydropyridines (nifedipine).	Negative inotropic effects may cause cardiac decompensation.	Avoid all except amlodipine and felodipine.
CNS stimulants e.g. epinephrine, pseudoephedrine.	Can cause hypertension, tachycardia, arrhythmias.	Use with caution.
Glitazones e.g. rosiglitazone, pioglitazone.	Associated with significant fluid retention, weight gain and pulmonary oedema.	Use with caution. Avoid in NYHA class III or IV heart failure.
Class I antiarrhythmics e.g. quinidine, procainamide, flecainide.	Have negative inotropic effects and can increase risk of serious arrhythmia.	Avoid.
Tricyclic antidepressants e.g. amitriptyline, imipramine.	Have Type IA antiarrhythmic properties and may worsen conduction delays.	Use with caution. SSRI is anti- depressant drug of choice.
Licorice (herb).	Has aldosterone-like action and enhances sodium retention.	Avoid.
Drugs with high sodium content e.g. laxatives containing sodium phosphate (Fleet®).	Exacerbate oedema due to increased plasma sodium.	Use alternatives.

APPENDIX

A. Management and goals for patients with concomitant hypertension[138]

- Lifestyle and dietary modification should apply. These include:
  - Smoking cessation
  - Weight management
  - Limitation of alcohol consumption
  - Reduction in intake of salt
  - Reduction in intake of cholesterol and saturated fats
  - Maintenance of adequate intake of dietary potassium
  - Increased physical activity

- BP < 140/90 mmHg.

- Diabetes mellitus and chronic renal disease - BP < 130/80mmHg.

- Elderly BP < 140/90mmHg (provided no orthostatic hypotension occurs).

B. Management and goals for patients with concomitant hyperlipidaemia [139]

- Lifestyle and dietary modification should apply. These include:
  - Smoking cessation
  - Weight management
  - Increased physical activity
  - Diet low in saturated fat and high in fibre
  - Limit alcohol and simple carbohydrates for patients with raised triglycerides (TG)

- Risk status should be assessed using the adapted Framingham Risk Score, and low density lipoprotein cholesterol (LDL-C) target should be set according to patient's risk (Refer to Table A).

- Cardiovascular risk equivalents include diabetes mellitus, stroke, peripheral artery disease, abdominal aortic aneurysm and established cardiovascular disease. These confer "high risk" status to patients and target LDL should be <2.6mmol/L (100mg/dL).

- Appropriate agent should be chosen for particular type of dyslipidaemia (Refer to Table B). First line agents include
  - Statins for raised LDL-C
  - Fibrates for raised TG
  - For mixed dyslipidaemias, use fibrate first-line if TG > 4.5mmol/L (400mg/dL). If LDL-C remains high, add statin. If LDL-C abnormality predominates, use statin as a first-line, and add fibrate if TG remains high or if the HDL remains unacceptably low.

Table A - Lipid Goal Levels for 3 Risk Groups[139] (Fasted lipid levels should be used, i.e. 10-12 hours overnight fast)

	High Risk Group	Intermediate Risk Group	Low Risk Group
LDL-C mmol/L (mg/dL)	<2.6 (100)	<3.4 (130)	<4.1 (160)
TG mmol/L (mg/dL)	<2.3 (200)	<2.3 (200)	<2.3 (200)
HDL-C mmol/L (mg/L)	≥1.0 (40)	≥1.0 (40)	≥1.0 (40)

An optional goal of LDL-C <2.1mmol/L may be considered for individuals with very high risk.

Table B - Drugs of Choice for Various Dyslipidaemias[139]

Dyslipidaemia	Drugs Of Choice
Hypercholesterolaemia	Statin ± Fibrate *
Mixed Dyslipidaemia	Statin ± Fibrate * or Fibrate * ± Statin
Hypertriglyceridaemia	Fibrate *
Severe Hypertriglyceridaemia	Fibrate * + Omega 3 Fish Oil
Isolated low HDL-C	Fibrate *

* For patients in whom fibrates are indicated, nicotinic acid may also be used.

C. Management and goals for patients with concomitant diabetes mellitus[140]

- Lifestyle and dietary modification should apply. These include:
  - Weight management.
  - Physical activity and exercise (This may not be appropriate in patients with severe heart failure).
  - Nutrition plan, saturated fat of less than 10% total calories, carbohydrate 50-60% total calories, protein 15-20% total calories.
  - Abstinence from alcohol for poorly-controlled diabetics and overweight individuals, and especially if concomitant hypertriglyceridaemia.
  - Sweeteners permitted in safe daily limits.
  - Smoking cessation.

- Refer to Table C for targets of glycaemic control.

Table C - Targets of Glycaemic Control[140]

Test	Assessment of Glucose Control			
	Ideal (non-diabetic levels)	**Optimal (target goal for majority of patients)**	**Suboptimal (adequate goal for some patients)**[δ]	**Unacceptable (action needed in all patients)**
HbA_{1c}[*] (%)	4.5-6.4	6.5-7.0	7.1-8.0	>8.0
Pre-meal glucose[+] (mmol/l)	4.0-6.0	6.1-8.0	8.1-10.0	>10.0
2-hour post-meal glucose[+] (mmol/l)	5.0-7.0	7.1-10.0	10.1-13.0	>13.0

***** Normal reference range obtained from NUH and SGH laboratories using Biorad Variant II_R. Other laboratories should establish their own non-diabetic reference intervals.

+ Values pertaining to capillary blood sample.

δ Adequate goal in elderly patients and individuals with advanced diabetic complications or other co-morbidities.

LIST OF ABBREVIATIONS

AA :	Aldosterone Antagonists
ACE-I :	Angiotensin-Converting Enzyme Inhibitors
ARB :	Angiotensin-II Receptor Blockers
AV :	Atrioventricular
β-blocker :	Beta-adrenergic blockers
BP :	Blood Pressure
CCB :	Calcium Channel Blockers
CNS :	Central Nervous System
COX-2 inhibitors :	Cyclooxygenase-2 inhibitors
CrCl :	Creatinine Clearance
EF :	Ejection Fraction
GFR :	Glomerular Filtration Rate
HbA_{1c} :	Glycosylated haemoglobin
HDL-C :	High Density Lipoprotein Cholesterol
IV :	Intravenous
LDL-C :	Low Density Lipoprotein Cholesterol
LV :	Left Ventricular
LVEF :	Left Ventricular Ejection Fraction
NSAIDs :	Non-Steroidal Anti-Inflammatory Drugs
NYHA :	New York Heart Association
SSRI :	Selective Serotonin Re-uptake Inhibitor
TG :	Triglycerides
TZD :	Thiazolidinediones

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ISBN: 978-981-05-9116-8