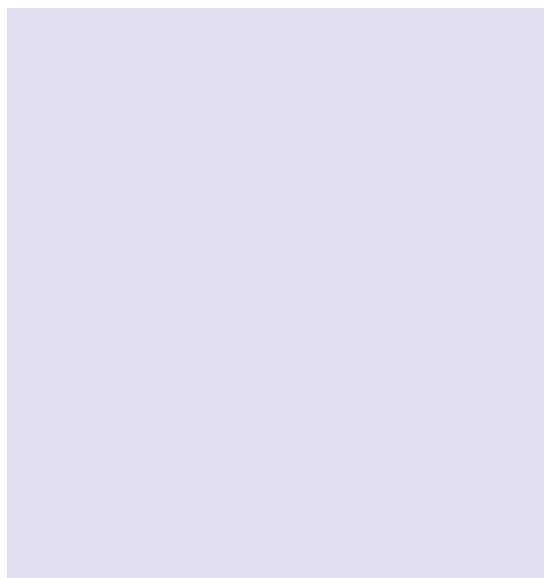


CHRONIC HEART FAILURE

— *management of the disease*

By MOJGAN SANI, DPHARM, MBA, MRPHARMS

The second article in this month's special feature deals with the pharmacological management of patients with chronic heart failure. NICE guidelines and non-pharmacological management are also covered



SHEILA TERRY/SPL

*Digoxin is derived from the foxglove plant (*Digitalis purpurea*)*

Goals related to the management of chronic heart failure patients may include prevention (blood pressure control, secondary prevention post myocardial infarction [MI]), symptom reduction, prevention of progression of disease, prolonging survival and reduction of resource use and hospital admission.

Prevention The American College of Cardiology (ACC) and the American Heart Association (AHA) published guidelines in 2001 with an approach to the classification of chronic heart failure and progression of the disease.¹ Stage A consists of patients at high-risk of developing chronic heart failure but with no structural abnormality. Stage B includes patients with known structural abnormalities leading to chronic heart failure but no symptoms. Stage C refers to patients with symptoms of chronic heart failure and stage D consists of end-stage heart failure patients.

The recommendation for the prevention of chronic heart failure in stage A patients is meticulous control of hypertension (particularly systolic hypertension in the elderly) and secondary prevention thera-

pies such as lipid-lowering drugs and angiotensin converting enzyme (ACE) inhibitors in patients at high-risk of vascular events. Secondary prevention therapy such as ACE inhibitors, beta-blockers, antithrombotics and lipid-lowering agents are recommended in post-infarction patients.

Symptom control Symptoms can be minimised by correcting the underlying haemodynamic abnormalities causing volume retention. Therefore, measures such as salt restriction, reduction in ventricular filling pressures (by diuretics) and improving cardiac output (digoxin, ACE inhibitors, other vasodilators) can be effective.

Prevention of disease progression Remodelling is defined as the process of progressive left ventricular dysfunction and dilatation. Both inhibition of the renin-angiotensin-aldosterone system and the use of beta-blockers seem to prevent and, to some extent, reverse the remodelling process.

Prolong survival Drug therapies such as ACE inhibitors, beta-blockers and spironolactone have been shown to prevent or slow the progression of the disease, thereby prolonging survival in heart failure patients.²⁻⁷

PHARMACOLOGICAL THERAPY

This article reviews the pharmacological options for the treatment of chronic heart failure. Table 1 (p96) presents a summary of the drugs available to treat chronic heart failure, and Table 2 (p97) lists common side effects of these drugs according to NICE guidance.

DIURETICS

Diuretics are used for the treatment of pulmonary and peripheral oedema in heart failure patients. They reduce symptoms, hospital admission and improve exercise performance, although there have been no long-term trials conducted that have investigated the impact of diuretics on mortality in chronic heart failure patients.

Thiazides can be used in mild chronic heart failure but are less potent since they act on the cortical diluting segment of the distal tubule which is responsible for reabsorption of only 10 per cent of filtered sodium. They have a duration of action of between 12 and 24 hours and have a flat dose response curve, the maximum effective dose of bendroflumethiazide being 5mg.

Loop diuretics are the mainstay of therapy because they are the most potent diuretic group and are active at low glomerular filtration rates (GFR). They act on the thick ascending loop of Henle where about 25 per cent of the sodium in the glomerular filtrate

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is reabsorbed. Therefore, loop diuretics have a much higher ceiling natriuretic action than the thiazides. They are also more likely to cause hypovolaemia in the short term.

Metolazone is a thiazide-like diuretic and has a unique property. It retains efficacy when other thiazides become ineffective at GFR less than 30 ml/min. The combination of metolazone and furosemide is useful in patients with refractory chronic heart failure who fail to respond to large doses of furosemide alone.

Both loop and thiazide diuretics increase Na^+ delivery to the distal nephron and therefore enhance Na^+/K^+ exchange. Most patients with chronic heart failure have symptoms of Na^+ and fluid retention and will therefore require diuretic therapy. When the fluid retention is mild a thiazide may be the preferred agent, because they have a less abrupt onset and a longer duration of action. They are also more effective antihyperten-

sive agents. In patients who have moderate to severe chronic heart failure, or if the GFR is severely impaired, loop diuretics are better options for treatment. Metolazone may be used for the management of diuretic resistance.

Diuretics are essential for symptom control but treatment has its drawbacks such as electrolyte imbalance, eg, hypokalaemia, hypomagnesaemia, etc. Patients should be carefully monitored for potential side effects.

— ACE INHIBITORS

ACE inhibitors have provided a major advance in the management of chronic heart failure by inhibiting conversion of angiotensin-I to angiotensin-II. Angiotensin-II is responsible for an increase in systemic vascular resistance (systemic vasoconstriction), stimulation of peripheral

and central effects of the sympathetic nervous system, water and sodium retention and enhancing vasopressin synthesis. ACE inhibitors have been shown to improve symptoms and exercise tolerance and to prolong survival in chronic heart failure patients and in asymptomatic and post-myocardial infarction patients with left ventricular systolic dysfunction.^{1,3,8}

On the basis of the evidence from ACE inhibitor trials, patients with symptomatic chronic heart failure or asymptomatic left ventricular ejection fractions less than 40 per cent should be treated.^{1,3}

Patients with severe chronic heart failure who are also on diuretics often have hyponatraemia and high plasma renin activity. These patients respond well to ACE inhibitors but caution is needed because of the risk of hypotension.

The double-blind placebo controlled CONSENSUS (cooperative new scandinavian)

vian enalapril survival study) study showed a significant mortality benefit with ACE inhibitors in patients with severe chronic heart failure.⁹ It also showed a reduction in heart size and improvement in NYHA classification (see Sani M. Chronic heart failure — diagnosis of the disease. *Hospital Pharmacist* 2004;11:87-91). The SOLVD (studies of left ventricular dysfunction) trial demonstrated further mortality and morbidity reductions with ACE inhibitors in patients with mild to moderate chronic heart failure (left ventricular dysfunction).² Hospital readmission was also reduced, making therapy cost effective.^{2,9}

ACE inhibitors are generally safe and well tolerated. Contraindications include pregnancy, history of angioedema, bilateral renal artery stenosis and hyperkalaemia. Among side effects of ACE inhibitors are dizziness, hypotension, chronic non-productive cough and skin rashes.

■ ANGIOTENSIN-II ANTAGONISTS

These drugs improve haemodynamic measurements in patients with or without concomitant use of ACE inhibitors. The ELITE (evaluation of losartan in the elderly) trial used losartan in heart failure patients and showed a lower number of deaths in the losartan group compared with placebo.¹⁰ ELITE II, however, did not show that losartan was superior to captopril in prolonging survival in chronic heart failure patients.¹¹

The Val-HeFT (valsartan heart failure trial) evaluated the effect of valsartan on optimally treated heart failure patients (85 per cent already on an ACE inhibitor and 34 per cent on a beta-blocker). There was no difference in overall survival but it showed significant mortality and morbidity reductions in the group of patients who were not on ACE inhibitors. This study demonstrated the benefit of angiotensin-II receptor antag-

onists in patients who are unable to take ACE inhibitors.¹²

The VALIANT (valsartan in acute myocardial infarction) trial compared the effects of valsartan with captopril and with a combination of the two drugs in MI patients with left ventricular systolic dysfunction. The authors concluded that valsartan was as effective as captopril in high-risk patients post-MI and that combination therapy increased the risk of adverse events without improving survival.¹³

CHARM (candesartan in heart failure — assessment of reduction in mortality and morbidity) was a programme to investigate the clinical usefulness of the long-acting angiotensin-II receptor antagonist, candesartan, in a broad spectrum of patients with symptomatic heart failure.¹⁴ The programme recruited over 7,000 heart failure patients. Patients had classic symptomatic heart failure (depressed left ventricular systolic function [LVEF] <40 per cent) and

Table 1: NICE recommendations of pharmacological therapies for patients with heart failure due to left ventricular systolic dysfunction

Diuretics	Should be routinely used for the relief of congestive symptoms and fluid retention, titrated up or down according to needs
ACE inhibitors	Should be used in all patients with heart failure due to LV systolic dysfunction. The initiation of therapy should be before a beta-blocker, titrated up at short intervals (every two weeks) to reach optimal tolerated or target dose, with blood biochemistry measured after initiation and at each dose increment
Beta-blockers	Licensed beta-blockers should be initiated in patients with heart failure due to LV systolic dysfunction after diuretics and ACE inhibitors have been given, regardless of whether symptoms persist or not. The initiation should follow in a "start low, go slow" manner with assessment of heart rate, blood pressure and clinical condition after each stage of titration. If a patient is already on a beta-blocker for a concomitant condition, eg, angina or hypertension, they may continue with their existing beta-blocker or change
Aldosterone antagonists	Patients with heart failure due to LV systolic dysfunction who remain symptomatic despite optimal therapy should be prescribed an aldosterone antagonist. Blood potassium levels should be monitored closely to avoid hyperkalaemia
Digoxin	Digoxin is recommended for worsening or severe heart failure due to LV systolic dysfunction despite ACE inhibitor, beta-blocker and diuretic therapy. If atrial fibrillation is present, then all patients with any degree of heart failure should be on digoxin
Angiotensin-II receptor antagonists	Angiotensin-II receptor antagonists should be used if patients are intolerant of ACE inhibitors (refer to the CHARM study which was published after this guidance had been written)
Amiodarone	Prescribing should be in consultation with a specialist. If prescribed, then a six-monthly clinical review (liver, thyroid function and tests for other side effects) is recommended
Anticoagulants	Anticoagulant therapy is recommended in patients with atrial fibrillation. If the patient is in sinus rhythm, anticoagulation is recommended only in those with a history of thromboembolism, left ventricular aneurysm or intracardiac thrombus
Aspirin	Low dose aspirin should be prescribed in patients with a combination of heart failure and atherosclerotic arterial disease, eg, coronary heart disease
Statins	Statins are prescribed if heart failure patients have known atherosclerotic vascular disease
Isosorbide/hydralazine combination	Isosorbide/hydralazine combination may be used in patients with heart failure who are intolerant of ACE inhibitors or angiotensin-II receptor antagonists

were randomised into two trials — either an ACE inhibitor intolerant population (CHARM alternative), or a population treated with ACE inhibitors (CHARM-added). In addition, patients with preserved LV function (LVEF > 40 per cent) were also randomised into a third trial (CHARM-preserved). All patients received candesartan or placebo. CHARM-alternative showed that in patients who were not taking ACE inhibitors due to previous intolerance, candesartan significantly reduced the risk of cardiovascular death or hospital admission for chronic heart failure, with an overall risk reduction of 23 per cent ($P < 0.0004$). CHARM-added showed that in patients who were prescribed medicines including an ACE inhibitor, an additional mortality benefit was observed if candesartan was added to therapy. The additional risk reduction for cardiovascular mortality and

hospital admission was 15 per cent ($P = 0.011$) when compared with conventional therapy. In the CHARM-preserved programme, the primary endpoint of cardiovascular death or hospital admission due to chronic heart failure showed a trend of an 11 per cent risk reduction ($P = 0.018$).

— ALDOSTERONE ANTAGONISTS

A major breakthrough has been the strong recommendation to add 25mg spironolactone for patients with class III and IV heart failure in view of the evidence from the RALES (randomized aldactone evaluation) study.⁷ The study showed a 30 per cent reduction in the risk of death among the class III or IV heart failure patients (ejection fraction <35 per cent) already being treated with loop diuretics, ACE inhibitors and digoxin. The rate of hospital admission was

also significantly reduced when spironolactone was added to the therapy. Routine use of spironolactone is not recommended in milder heart failure patients but it may be reasonable to use this agent in place of potassium replacement if there is diuretic-induced hypokalaemia.

The main concern with spironolactone is hyperkalaemia, and close monitoring is recommended. It may cause gynaecomastia and other androgenic effects. Another aldosterone antagonist, eplerenone, is being studied in clinical trials and may have a better side effect profile since it has a lower affinity for androgen and progesterone receptors.

— BETA-BLOCKERS

Beta-blockers have a major role in the management of patients with heart fail-

ure (class I to IV), with maximal effect in patients with concurrent ischaemic heart disease and dilated cardiomyopathy.

Activation of the sympathetic nervous system in chronic heart failure and its adverse prognostic effect have been recognised over the years. High concentrations of catecholamines are known to cause acute and chronic myocardial damage.

Over 14,000 patients with chronic heart failure have been studied in randomised placebo-controlled trials of beta-blockers, providing evidence for improved morbidity and survival.^{15,16} The three large clinical trials used bisoprolol and metoprolol: CIBIS I (coronary insufficiency bisoprolol study), the CIBIS II trial and the MERIT-HF (metoprolol randomised intervention trial in heart failure) trial.^{4,5,17} Other trials used the non-selective beta-blocker carvedilol: COPERNICUS (carvedilol prospective randomised cumulative survival study) and the US Carvedilol Trials.¹⁸⁻¹⁹ In all studies beta-blockers produced significant reductions in mortality and chronic heart failure hospital admissions. The CAPRICORN (carvedilol post-infarct survival control in left ventricular dysfunction) study in patients after MI with a mean ejection fraction of 33 per cent also showed a significant reduction in mortality.²⁰

It is now well accepted that beta-blockers cause a decrease in sudden cardiac deaths

and increase survival in patients post-MI, and this beneficial result may be obtained in patients with varying grades of heart failure.

The side effects of beta-blockers are well known, eg, dizziness, hypotension, worsening of dyspnoea, bradycardia. The main additional concern in heart failure is the potential for early deterioration in patients who are relying on adrenergic activity for compensation. The key to the successful use of beta-blockers in chronic heart failure patients includes selection of appropriate patients, initiation of treatment at low doses and gradual up-titration with close monitoring.

In general, patients should be stable and there should be no fluid overload, with diuretics and ACE inhibitors initiated and stabilised.

DIGOXIN

Digoxin binds to and competitively inhibits the Na⁺/K⁺ATPase on the cardiac myocyte cell membrane and in other tissues. Digoxin is indicated for all patients with impaired systolic function and NYHA class II, III and IV chronic heart failure.²¹ Patients with NYHA class II chronic heart failure are managed with diuretics and ACE inhibitors. Recurrence of chronic heart failure is an indication for the addition of

digoxin. The Digitalis Investigation Group did not show a significant decrease in total mortality.²¹ However, there was a trend towards a decrease in the risk of death attributed to worsening chronic heart failure. The risk related to the combined outcome of death and hospital admission was significantly lower in the digoxin group. In essence, the study indicated that digoxin significantly decreases death or hospital admission caused by worsening heart failure in patients with class II, III and IV heart failure and an ejection fraction <25 per cent.

The RADIANCE (randomized assessment of digoxin and inhibitors of angiotensin converting enzyme) study investigated the combination of digoxin with diuretics and ACE inhibitors during which digoxin was withdrawn for three months.²² The study showed a significant worsening of chronic heart failure in the group when digoxin was withdrawn. They concluded that it would be rational to use the triple combination therapy of diuretics, ACE inhibitors and digoxin to manage left ventricular failure and improve symptoms, survival and quality of life in patients with class II, III and IV chronic heart failure.

Digoxin toxicity has become relatively uncommon with improvements in the understanding of dosing and monitoring

Table 2: Major complications of drug therapy

Diuretics	Common: postural hypotension, gout, urinary urgency Serious: electrolyte imbalance (hypokalaemia, hypomagnesa, hyponatraemia), arrhythmia
ACE inhibitors	Common: cough, hypotension including postural Serious: worsening renal function, renal infarction in renal artery stenosis, angio-oedema
Beta-blockers	Common: tiredness, bradycardia, coldness Serious: asthmatic attack, exacerbation of heart failure, heart block
Spirolactone	Common: gynaecomastia, tiredness, rashes Serious: hyperkalaemia, hyponatraemia
Digoxin	Common: nausea Serious: life threatening arrhythmias
Angiotensin-II receptor antagonists	Common: hypotension including postural Serious: worsening renal function, renal infarction in renal artery stenosis
Amiodarone	Common: photosensitivity, nausea, thyroid dysfunction, sleep disturbance, corneal microdeposits Serious: thyrotoxic storm, pro-arrhythmia, pulmonary/hepatic fibrosis
Inotropes	Common: nausea, palpitations Serious: arrhythmia, cardiotoxicity

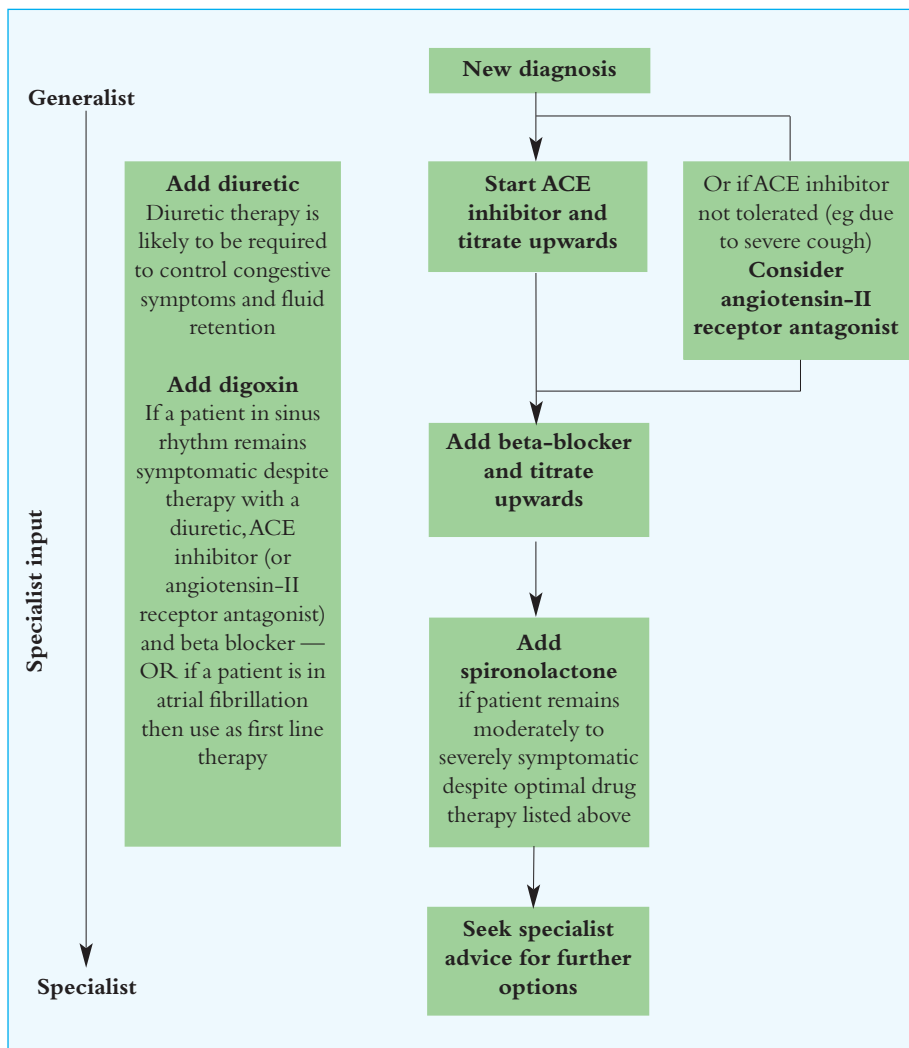


Figure 1 : Algorithm for the pharmacological treatment of symptomatic heart failure due to LV systolic dysfunction. (Reproduced by permission of the Royal College of Physicians)

drug levels. The most important form of toxicity is arrhythmias, especially in hypokalaemic patients. Other less serious adverse effects include nausea and visual disturbances.

— DIRECT-ACTING VASODILATORS

Agents that dilate the arteriolar vessels can reduce left ventricular after-load and agents that dilate the venous bed reduce left or right ventricular pre-load. This will result in the reduction in left and right atrial pressures, thereby improving dyspnoea and oedema.

The V-HeFT-I (vasodilator heart failure) trial, was the first large scale trial to evaluate the clinical efficacy of direct vasodilators (prazosin or combination of hydralazine and isosorbide dinitrate). The latter combination therapy reduced mortality but prazosin showed no benefit in survival.²³ However, the subsequent V-HeFT-II trial comparing isosorbide dinitrate-hydralazine combination with enalapril, showed that an even more significant reduction was observed in the ACE inhibitor group.²⁴

Despite the favourable results of V-HeFT-I, the role of direct acting vasodilators is limited due to the higher benefits and evidence in support of ACE inhibitors. For patients who do not tolerate ACE inhibitors, an angiotensin-II receptor antagonist is the first alternative (because of better tolerability) compared with nitrate-hydralazine combination. However, nitrates are safe and effective for the treatment of angina in chronic heart failure patients and hydralazine may be helpful in reducing severe mitral regurgitation.

Vasopeptidase inhibition with unlabeled drugs such as omapatrilat causes simultaneous inhibition of ACE and neutral endopeptidase leading to vasodilatation and sodium excretion, reduction in aldosterone and inhibition of sympathetic activity.

— ANTITHROMBOTIC THERAPY

Although anticoagulation is indicated in patients with chronic or intermittent atrial fibrillation or flutter due to a high-risk of embolic events, routine anticoagulation in patients in sinus rhythm is not recommended.

The hypothesis of aspirin use as an antithrombotic in heart failure patients and potential interaction with ACE inhibitors is currently being investigated in the WATCH (warfarin and antiplatelet therapy in chronic heart failure) trial, which is comparing warfarin, aspirin and clopidogrel in patients with chronic heart failure and sinus rhythm.

— ANTIARRHYTHMICS

Sudden death is responsible for 40–50 per cent of mortality in patients with chronic heart failure, often caused by ventricular tachyarrhythmias. Beta-blockers can prevent 40–50 per cent of the episodes of sudden death.¹⁵ The role of treatment with anti-arrhythmic agents and devices in this patient population remains controversial.

— NEWER AGENTS

There are a number of new agents currently being developed in order to restore the neurohormonal balance. Atrial and brain natriuretic peptides (ANP and BNP) are hormones with vasodilatory, natriuretic, diuretic and renin-angiotensin-aldosterone system suppressing properties. ANP and BNP are degraded by an enzyme, neutral endopeptidase (NEP). NEP inhibitors are being investigated for the management of chronic heart failure.

— NICE

NICE guidelines for diagnosis and management of chronic heart failure were published in July 2003.²⁵ Figure 1 shows an algorithm for the pharmacological treatment of symptomatic heart failure due to left ventricular systolic dysfunction.

The guidelines recommend that patients with symptomatic heart failure due to left ventricular dysfunction should be treated with diuretics for symptom control related to fluid retention. Once diagnosis is confirmed, all patients should be started on an ACE inhibitor and titrated upwards to the optimised evidence-based dose. Those patients who are intolerant to ACE inhibitors should be initiated on an angiotensin-II receptor antagonist. Beta-blocker therapy is then introduced in appropriately selected patients and titrated upwards to an optimised tolerable dose, paying particular attention to the slow titration to minimise potential intolerance to the agents. Patients should be carefully counselled and prepared for the possibility of early deterioration and need to persevere during the titration period. Spironolactone is then added to moderate to severely symptomatic patients despite optimal drug therapy. Digoxin is also used as first line therapy if the patient is in atrial fibrillation. If the patient is in sinus rhythm, however, digoxin may be introduced at a later stage if the

patient remains symptomatic despite drug therapy with a diuretic, ACE inhibitor (or angiotensin-II receptor antagonist) and a beta-blocker.

The guidelines have also made recommendations on rehabilitation programmes suggesting that advice on exercise, psychological support and other issues can be of great benefit to patients (Table 3).

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Table 3: General recommendations from NICE

Exercise	Patients with heart failure are to be encouraged to adopt regular aerobic exercise
Smoking	Patients are strongly advised not to smoke and smokers should be referred to smoking cessation services
Alcohol	Patients should be advised on alcohol consumption according to the clinical circumstances. If heart failure is related to alcohol the patients should abstain from drinking alcohol
Diet and nutrition	Advice on healthy nutrition should be offered. In heart failure patients it may be necessary to reduce weight and restrict fluid and salt intake
Vaccination	Patients should be offered an annual influenza vaccination and pneumococcal vaccination (only required once)

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