

Chronic heart failure

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Essentials

- The diagnosis and management of heart failure (HF) often calls for cooperation between primary and specialist care.
- Echocardiography should be performed to obtain information about the underlying cause of HF, its mechanism and severity. In principle, echocardiography is indicated for all patients who are going to start long-term medication to manage the condition.
- Patients with HF often have several coexisting conditions, which might complicate diagnosis and treatment.
- The aim should always be to target the underlying cause(s), e.g. hypertension, myocardial ischaemia, valvular disease or arrhythmia. All contributing diseases and conditions should also be identified and treated.
- The most important drug groups in secondary prevention, as far as prognosis and symptoms are concerned, are ACE inhibitors, angiotensin-II receptor antagonists (also known as angiotensin receptor blockers, i.e. ARBs) and beta-blockers, which are used in an asymptomatic phase and also in high-risk patients.
- Drug treatment to optimise the symptoms and prognosis requires close monitoring of the patient and will take several months.

In general

- HF is a complex syndrome in which the heart is unable to maintain adequate circulation to meet the body's normal needs. The dysfunction can be caused by a variety of cardiovascular diseases (table [1](#)), the most common ones being coronary heart disease, hypertension and valvular disease, either alone or in different combinations.
- Pump failure initiates neurohormonal compensatory mechanisms in the body which may, as the circulatory disturbance becomes chronic, contribute towards further worsening of cardiac function.
- Symptomatic HF affects 1–2% of the European adult population.
- The incidence of HF increases with advancing age. The prevalence of chronic HF is $\geq 10\%$ in persons over 70 years of age. 50% of the patients are ≥ 80 years of age.
- HF may be caused by impaired myocardial contractility (systolic HF; Heart Failure with reduced Ejection Fraction, HFrEF) or by the stiffening of the heart walls (diastolic HF; Heart Failure with preserved Ejection Fraction, HFpEF) or most often by a combination of the two.
 - In the entire population, the incidence rate of systolic and diastolic HF is almost equal.
 - In elderly individuals (over 80 years of age), the diastolic mechanism of HF is more common.
- If left untreated, the prognosis of HF is poor regardless of whether the failure is caused by systolic or diastolic dysfunction.
- In 30–50% of patients with the most severe form of HF (NYHA III–IV; table [4](#)), the disease progresses to death within one year after diagnosis. Many patients have other significant comorbidities.
- Well managed pharmacological therapy can significantly reduce the symptoms and improve prognosis.
- Diagnostics and management aims to
 - identify the existence of the condition, the underlying heart disease(s) as well as any contributing diseases and conditions
 - understand the mechanism of the failure
 - refer patients appropriately to specialist care for investigations and treatment
 - See also Acute heart failure .
 - follow the principles of good drug therapy
 - Medication to affect prognosis
 - Symptomatic medication

Causes and mechanism of HF

- Conditions leading to HF are listed in table [1](#).
- In *systolic HF* (Heart Failure with reduced Ejection Fraction, HFrEF) the myocardial contractility is impaired.
 - Ischaemic cardiomyopathy (coronary heart disease, i.e. CHD)
 - Hypertension
 - Valvular diseases (aortic stenosis and mitral regurgitation are the most common)
 - Cardiomyopathies (dilated, hypertrophic, restrictive cardiomyopathy)
 - Arrhythmias (fast atrial fibrillation [AF], sustained tachycardia)
- In *diastolic HF* (Heart Failure with preserved Ejection Fraction, HFpEF) the relaxation and/or passive elasticity of the left ventricle are impaired as is its ability to expand during diastole.
 - Left ventricular hypertrophy (LVH) associated with hypertension or advanced age
 - Ischaemic cardiomyopathy (CHD)
 - Restrictive cardiomyopathy (metabolic storage diseases, such as cardiac amyloidosis, haemochromatosis)

Table 1. Conditions leading to heart failure

Causes of heart failure	
The most common causes (80–90% of cases)	▪ CHD, hypertension and valvular disease, either alone or in combination
Rare causes	▪ Myocardial disease (cardiomyopathy, myocarditis) ▪ Pericardial disease (constriction, effusion) ▪ Congenital heart diseases ▪ Persistent tachycardia ▪ Chronic lung disease and ventilatory defect ▪ Pulmonary embolism and arterial pulmonary hypertension ▪ Arteriovenous shunt ▪ Cardiac tumour ▪ Tamponade ▪ Anaemia ▪ Hypothyroidism, hyperthyroidism ▪ Cardiotoxic drugs (many anticancer drugs, especially related to high cumulative doses of anthracyclines) ▪ Excessive prolonged alcohol abuse ▪ Illegal drugs

Treatment goals in HF

- Reduction of mortality
- Improvement of symptoms and quality of life
- Prophylaxis
 - Preventing the progress of myocardial damage
 - Preventing the worsening of symptoms
 - Reduction in the need for hospitalisation

Precipitating and exacerbating factors of HF

- Cardiovascular causes
 - Myocardial ischaemia, unstable angina
 - Tachyarrhythmias (fast AF)
 - Bradyarrhythmias (sick sinus syndrome, AV block)
 - Hypertension
 - Pulmonary embolism

- Other causes
 - Infections, e.g. pneumonia, systemic infection (sepsis)
 - Anaemia
 - Hyperthyroidism and hypothyroidism
 - Renal failure
 - Obesity
 - Problems associated with drug therapy
 - Non-adherence to cardiac medication
 - Excessive or continuous use of NSAIDs
 - Drugs that reduce myocardial contractility, such as verapamil, diltiazem, disopyramide (also beta-blockers if treatment is started with high doses)
 - Excessive salt and fluid intake
 - Excessive alcohol consumption
- See also table [1](#).

Diagnosis

- No single symptom or finding establishes the diagnosis of HF. Symptoms typical to HF, clinical findings as well as results from imaging studies are all used to diagnose HF. Cooperation with specialist care is therefore important already at the time of diagnosis since the patient will often need such imaging studies that are usually not within the realm of primary care.
- See tables [2](#) and [3](#).

Table 2. Diagnostic criteria of HF

Diagnostic criteria	Signs and symptoms
1. Patient has symptoms typical to HF or he/she is known to have a heart disease that predisposes to HF such as hypertension, coronary heart disease, sequelae of myocardial infarction, valvular disease.	▪ Dyspnoea at rest ▪ Abnormal fatigue during mild exertion or daily activities
2. Patient has clinical findings specific to HF	▪ Tachycardia ▪ Ventricular gallop ▪ Raised jugular venous pressure (JVP) ▪ Peripheral oedema ▪ Hepatomegaly ▪ Abnormal ECG (hypertrophy, Q waves, arrhythmias) ▪ Elevated natriuretic peptide concentration ▪ Chest x-ray demonstrating cardiomegaly and/or venous congestion
3. Imaging studies show structural and/or functional impairment of the heart (echocardiography, radionuclide ventriculography, MRI, left ventricular angiography)	

Table 3. Clinical diagnosis of HF

Diagnosis of HF		Other diseases and conditions to consider
is supported by	is opposed by	

Diagnosis of HF		Other diseases and conditions to consider
is supported by	is opposed by	
■ Reduced exercise capacity ■ Orthopnoea (dyspnoea when lying down) ■ Abnormal ECG (LVH, RVH, atrial strain, Q waves, tachycardia) ■ Raised JVP ■ Elevated BNP or proBNP ■ Chest x-ray demonstrates cardiomegaly and pulmonary congestion ■ Positive response to drug therapy (diuretic)	■ Normal ECG ■ Normal BNP/proBNP ■ Normal performance in clinical exercise test	■ Lung disease ■ Renal disease ■ Anaemia ■ Hypothyroidism/hyperthyroidism ■ Very advanced age

Symptoms

- Dyspnoea or abnormal fatigue during exercise or at rest
 - Orthopnoea and cough when lying down
 - Dyspnoea on exertion may also have other causes, the presence of which should be considered when obtaining the history and examining the patient. Other causes include: CHD, chronic obstructive pulmonary disease (COPD) or asthma, chronic pulmonary emboli, obesity, poor physical fitness or aging.
- Weight gain and oedema
 - These do not support diagnosis if they occur independently, but are of importance in the monitoring of treatment response.
- Loss of appetite is often associated with severe right-sided HF, development of ascites as well as liver and intestinal congestion.
- Cachexia (wasting of fat and muscle tissue) signifies advanced HF of long duration and poor prognosis.

Problems in differential diagnosis

- Severe obesity (BMI usually $\geq 35 \text{ kg/m}^2$)
- Poor physical fitness and lack of exercise
- CHD with dyspnoea on exertion as the main symptom
- Venous insufficiency causing ankle oedema (reduction of oedema with diuretics does not confirm the diagnosis of HF)
- COPD and exercise-induced asthma
- Pulmonary embolism and pulmonary hypertension

NYHA classification

- The overall functional capacity of a patient with chronic HF can be described with the New York Heart Association classification (NYHA classification); see table [4](#).
- The NYHA classification assesses the stage of HF and is suggestive of prognosis.
- The patient's functional capacity changes during the different stages of the disease and may improve with drug and device therapy, which should be documented in the patient's notes during follow-up visits.

Table 4. NYHA classification

NYHA class	Symptoms
NYHA I	No significant limitation of physical activity. Activities of daily living do not cause symptoms even though left ventricular dysfunction can be noted with echocardiography.
NYHA II	Limitation of physical activity. Strenuous physical activity results in dyspnoea or abnormal fatigue.
NYHA III	Marked limitation of physical activity. Less than ordinary physical activity results in dyspnoea or fatigue.
NYHA IV	All physical activity causes symptoms. Symptoms may also occur at rest.

Clinical findings [evd](#)

- Tachycardia ($> 90/\text{min}$), irregular rhythm (AF, frequent ectopic beats)
- Raised JVP
 - Distension of the internal jugular vein seen above the clavicle with the patient sitting up. Anatomic reasons may make it difficult to measure the JVP in some patients.
 - Can be measured more easily if gentle pressure is applied to the edge of the liver with the patient in semi-recumbent position (hepatojugular reflex).
- A third heart sound (ventricular gallop) in a patient over 40 years of age is suggestive of increased left ventricular filling pressure. Exertion, lateral position or elevation of the legs strengthens the third heart sound.
- Mitral regurgitation
- Hepatomegaly
 - The edge of the liver extends to below the costal margin and is tender on palpation.
- Pitting oedema of the lower limbs, which can also be due to many other aetiologies .
- Tachypnoea ($> 20/\text{min}$)
- Moist crackles and wheeze may be heard in severe and acute failure.
 - Wheeze and crackles may also be present due to an independent lung disease.

Additional investigations

ECG

- Changes related to an infarct scar (Q waves) and ST-T changes suggesting ischaemia also reveal the cause of HF.
- Hypertrophy (LVH, RVH, atrial strain)
- LBBB, duration of the QRS complex $> 120 \text{ ms}$
- Arrhythmias (AF, frequent ectopic beats, VT)
- A normal ECG is strong evidence against HF.

Laboratory tests

- Assist in differential diagnosis and identification of aggravating factors.
- May reveal the cause of failure and predict prognosis.
- Essential tests for the diagnostic work up include:
 - basic blood count with platelet count
 - plasma potassium, sodium, creatinine, eGFR (calculator [1](#))
 - ALT
 - fasting plasma glucose, HbA_{1c}
 - CRP
 - TSH
 - proBNP or BNP
 - troponin
 - lipids
 - ferritin, transferrin receptor (TfR), if anaemia or a history of iron deficiency is present
 - chemical urinalysis.
- The laboratory tests to be carried out during the follow-up phase are largely dependent on the drug therapies used and comorbidities (see Follow-up [1](#)).

Natriuretic peptides (BNP, proBNP and ANP) [evd](#)

- Increased atrial and ventricular filling pressures activate the synthesis and release of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP).
- The half-life of BNP, secreted by the ventricles, and its N-terminal fragment are longer than that of ANP, which is why ANP is not used in the diagnostic workup.
- A normal concentration of BNP ($< 100 \text{ pg/ml}$) and Nt-proBNP, i.e. N-terminal prohormone brain natriuretic peptide, ($< 400 \text{ pg/ml}$) exclude systolic dysfunction with over 90% certainty. A significantly increased concentration is highly suggestive of HF. See table [5](#).

- The proBNP concentration is higher in women than in men, and the concentrations increase with age. Laboratories therefore report the normal reference values separately for both sexes and age groups.
- The BNP concentration also increases with age and is higher in women than in men. However, the difference is smaller than with proBNP.
- Slightly elevated concentrations form a diagnostic "grey area".
 - Slightly elevated BNP concentrations occur in conditions which increase right ventricular pressure, e.g. asthma, COPD and pulmonary embolism.
 - Slight increases may also be seen in asymptomatic aortic stenosis, LVH, renal failure, hepatic cirrhosis and hypervolaemia due to various aetiologies. Fast arrhythmias (AF) increase ANP and BNP concentrations.
 - A new drug used in the treatment of HF, a combination of an angiotensin receptor blocker (ARB) and a neprilysin inhibitor, increases BNP concentrations.
- Very high BNP concentrations reflect the severity of the failure and poor prognosis.
- In addition to diagnosis, BNP can also be used for the monitoring of treatment response.

Table 5. The use of BNP and proBNP in the diagnosis of HF. The diagnosis is also based on clinical findings, ECG and chest x-ray.

BNP and proBNP concentration	Interpretation
▪ BNP < 35 pg/ml ▪ proBNP < 125 pg/ml	HF is unlikely; look for other causes of the symptoms.
▪ BNP ≥ 35 pg/ml ▪ proBNP ≥ 125 pg/ml	Further investigations necessary ** See abnormal and slightly elevated concentrations below.
BNP/proBNP abnormal or slightly elevated (within the "grey area")	
▪ BNP 100–400 pg/ml ▪ proBNP 300–2 000 pg/ml	Uncertain diagnosis; findings should be related to clinical symptoms and sex- and age-specific reference values taken into account. However, further investigations are often necessary **.
▪ BNP > 400 pg/ml ▪ Nt-proBNP > 2 000 pg/ml	Chronic HF likely * Further investigations necessary **
1. * The reference values are according to the 2016 ESC recommendations. Interpretation should also take into account the method, age and sex specific reference values supplied by the laboratory. 2. ** Echocardiography indicated	

Spirometry

- Spirometry should be carried out routinely in all patients with dyspnoea.
- A patient with HF may also have a lung disease that requires treatment.
- If pulmonary congestion is evident during clinical examination or on chest x-ray, it must be treated before spirometry is carried out.

Imaging studies

Chest x-ray [evd](#)

- Whenever possible an erect chest x-ray in two planes should be obtained.
- Cardiomegaly can be estimated by measuring the ratio of the heart silhouette to the maximum width of the thoracic cavity (cardio-thoracic ratio).
 - A ratio above 0.5 is abnormal.
 - Cardiomegaly may be absent in acute HF.

- The assessment of pulmonary vascular congestion may reveal the following: increased vascular markings particularly in the upper lung fields, prominent lung fissures and Kerley B lines.
- In severe HF, the x-ray may show interstitial oedema (bilateral hazy shadowing) and fluid in the pleural recesses.
- The interpretation of mild vascular congestion may be difficult from isolated x-rays, particularly if other changes due to chronic lung disease (fibrosis, scarring) are present.
- For the interpretation of a chest x-ray, see also .

Echocardiography

- An essential imaging study for the confirmation of the diagnosis of HF. It will also assist in the assessment of the mechanism and severity of the disease, and it will often provide essential information on the aetiology (see).
- According to care guidelines, echocardiography should be performed in all patients with a clinical diagnosis of HF. The study is discretionary in cases where the possible additional information yielded by the study would not change the treatment decisions already made (e.g. if, due to severe comorbidities, treatment is to concentrate on symptom relief only).
- Echocardiography is indicated for all younger patients with HF and those older patients in whom the diagnosis, aetiology or severity of the failure remains unclear.
- Echocardiography differentiates between systolic and diastolic HF.
 - In systolic dysfunction (HFrEF) the left ventricular ejection fraction (EF) is under 40–45%, and in diastolic dysfunction (HFpEF) it usually is over 45–50%.
 - EF refers to the ratio between stroke volume (SV = the volume of blood ejected from the left ventricle by each contraction) and left ventricular end-diastolic volume (EDV, end diastolic volume).
 - The detection of diastolic dysfunction with echocardiography is more complex. In addition to showing normal systolic function ($EF > 45\text{--}50\%$), echocardiography is used in these cases to show abnormal left ventricular relaxation and diastolic stiffness (tissue imaging, $e/E' \geq 13$, $E' < 9 \text{ cm/s}$), increase in left ventricular mass (LMVI men $\geq 115 \text{ g/m}^2$, women $\geq 95 \text{ g/m}^2$) and left atrial volume (LAVI $> 34 \text{ ml/m}^2$).
- Echocardiography allows indirect estimation of the left ventricular filling pressure and pulmonary artery pressure.

Indication for specialist consultation and investigations

- Severe HF may possibly be diagnosed with clinical investigations available in primary care, but in order to verify the mechanism of the failure specialist investigations are needed (echocardiography). If the condition stabilises with pharmacological therapy, additional investigations need not be carried out urgently.
- In mild failure, there usually is no hurry to reach exact diagnosis, and the diagnostic workup may progress systematically; the physical examination should be supplemented with laboratory and imaging studies, exclusion of other conditions and trying out pharmacological therapy.
- Mild left ventricular dysfunction may be almost asymptomatic, and only echocardiography will confirm the diagnosis.
- Specialist consultation regarding the underlying condition and its treatment is indicated if the patient is suspected to have CHD warranting revascularisation, valvular disease requiring surgery or arrhythmias needing electrophysiological management.
- In addition to heart disease, many other factors have an impact on clinical findings making it more difficult to reach diagnosis and plan treatment. Specialist consultation may be indicated in these cases.
- Diagnostics, starting medication and the titration of the medication call for patience both from the patient and the physician. Several appointments are usually needed. The treatment of unstable HF that is symptomatic at rest should be started in a hospital ward (NYHA classes III–IV, table 4).

Treatment of systolic HF

Non-pharmacological treatment [evd](#)

- Lifestyle education and counselling
 - Avoidance of obesity

- Reduction in salt intake
- Regular exercise
- Fluid restriction (1.5–2 l) in severe HF (NYHA III–IV symptoms)
- Smoking cessation
- Moderate alcohol consumption
- Obtaining and maintaining vaccination cover (pneumococci, influenza)
- Management of aggravating factors and coexisting diseases (e.g. infections, anaemia, diabetes, thyroid dysfunction, renal failure and COPD)
- Treatment of the underlying cause, e.g. revascularisation in CHD, valve surgery, restoring sinus rhythm, insertion of a pacemaker
- Coordination of patient education and monitoring through the chain of care within the local healthcare system. A specialist nurse intervention and addition of home care to monitor pharmacological therapy and disease progress.

Pharmaceutical therapy to improve prognosis

Drugs affecting the renin-angiotensin-aldosterone (RAA) system [evd](#)

- ACE inhibitors and ARBs
 - Improve prognosis in mild, moderate and severe HF as well as in HF due to myocardial infarction, even in asymptomatic patients.
 - Salt restriction and diuretics enhance the effect of ACE inhibitors.
 - The response to therapy is slow.
 - If ACE inhibitors are not suitable due to adverse effects, ARBs can be used instead; scientific evidence exists on their parity with ACE inhibitors.
 - Combination of an ARB and a neprilysin inhibitor
 - Improves prognosis in moderate and severe HF.
- Mineralocorticoid receptor antagonists (spironolactone and eplerenone)
 - Improve prognosis in severe (NYHA III–IV) systolic HF when combined with an ACE inhibitor and beta-blocker
 - Reduce the incidence of sudden death
 - May cause hyperkalaemia, worsen renal failure and increase the incidence of arrhythmias.

Drugs affecting the sympathetic nervous system [evd](#)

- Beta-blockers
 - Improve prognosis in mild, moderate and severe systolic HF.
 - Patients with ischaemic heart disease will particularly benefit from beta-blockers.
 - The response to therapy is slow; HF symptoms may worsen temporarily at the beginning of treatment.
 - Prevent sudden death.

Symptomatic drug treatment [evd](#)

- A diuretic is the first-line symptomatic drug in pulmonary congestion and peripheral oedema. The response is individual and may occur quickly depending on the drug and formulation used. The dose needed initially will be larger than the doses required during maintenance therapy, when minimum effective doses should be used.
- Ivabradine can be used to alleviate HF-induced symptoms in patients with systolic heart failure (NYHA II–IV), if they are in sinus rhythm and have a heart rate of over 75/min despite optimal prognosis-improving drug therapy (a beta blocker and an ACE inhibitor).
- Digoxin is indicated to optimise the ventricular rate in AF if beta blockers have not provided sufficient treatment response as well as to improve symptoms in severe HF (NYHA III–IV) in addition to other optimal drug therapy.
- Nitrates can be used in angina and as a first aid measure during an acute phase to treat pulmonary oedema (see Treatment of acute heart failure).
- Calcium-channel blockers amlodipine and felodipine can be used if the patient has coexisting hypertension that is not adequately controlled with an ACE inhibitor, or an ARB, and beta-blocker.

Diastolic HF

- The left ventricular systolic function (contractility) remains almost normal (EF > 45–50%) but left ventricular diastolic filling and wall relaxation are impaired (HFpEF).
- Can only be confirmed with echocardiography.
- Diastolic dysfunction is usually associated with myocardial ischaemia and occurs in conjunction with systolic dysfunction.
- May occur independently in association with LVH and increased fibrosis (hypertension, hypertrophic cardiomyopathy, aging heart) or myocardial infiltration (amyloidosis, haemochromatosis).
- HFpEF is more common than systolic dysfunction in women and the elderly.
- HFpEF should be suspected when the main presenting symptom is dyspnoea on exertion and
 - the patient is elderly (> 75 years) or has ischaemic heart disease or hypertension
 - ECG shows signs of LVH
 - signs of failure become evident during a fast rhythm (exertion, an episode of AF)
 - chest x-ray shows normal or near normal heart size.

Treatment

- Targets the underlying disease.
- There is little scientific evidence on the prognostic effects and on the efficacy of drug therapy.
- The principles of drug therapy do not greatly differ from those in systolic HF, except as regards the use of diuretics.
- A diuretic is a first-line drug if fluid retention is present.
- The diuretic effect must be actively assessed and the development of hypovolaemia avoided (symptoms may include dizziness, confusion, tachycardia).
- Heart rate should be promptly slowed with a beta-blocker.
- An active attempt should be made to maintain sinus rhythm.
- If in AF, ventricular rate should be controlled with a beta-blocker and anticoagulation started in risk groups
- The ARB candesartan and the ACE inhibitor perindopril have been noted to reduce symptoms but have no effect on mortality.
- Drug treatment of diastolic dysfunction does not improve symptoms or prognosis as much as does the treatment of systolic dysfunction.

Drug choice and use in HF

- ESC Guidelines 2016 [1](#)

ACE inhibitors and ARBs [evd](#)

- ACE inhibitors inhibit the formation of angiotensin II, and ARBs block the binding of angiotensin II to its target receptor (AT1 receptor).
- Irrespective of the severity of HF, these agents improve prognosis and reduce hospital admissions.
- Should be used in all patients with HF irrespective of the severity of the condition, including asymptomatic patients in whom left ventricular dysfunction has been diagnosed.
- Treatment is initially started with an ACE inhibitor, but if it is not tolerated due to adverse effects (usually a troublesome cough) an ARB can be used.
- The starting dose must not be used as the maintenance dose. The target dose should be in accordance with the latest study results, unless not tolerated due to the appearance of adverse effects. Drug dosages: see table [6](#).
- Contraindications to treatment include the following: a history of angio-oedema caused by an ACE inhibitor or ARB, bilateral renal artery stenosis, pregnancy and lactation.
- Treatment must not commence if the baseline creatinine concentration in the blood is > 220 µmol/l and potassium > 5.5 mmol/l.
- As soon as the creatinine level exceeds 160 µmol/l particular caution should be exercised when considering starting treatment, and individual consideration should be given to starting the treatment in a clinic or hospital specialized in HF treatment.

- Potassium concentration should remain under 5.5 mmol/l during treatment and creatinine under 220–250 µmol/l.

Table 6. Dosage of ACE inhibitors and ARBs (mg/day)

Drug	Starting dose	Maintenance/target dose
<i>ACE inhibitors</i>		
Captopril	6.25 mg three times daily	50 mg three times daily
Enalapril	2.5 mg twice daily	20 mg twice daily
Lisinopril	2.5–5 mg once daily	20 mg once daily
Ramipril	2.5 mg once daily	5 mg twice daily
Perindopril	2 mg once daily	4 mg once daily
<i>ARBs</i>		
Candesartan	4–8 mg once daily	32 mg once daily
Valsartan	40 mg twice daily	160 mg twice daily
Losartan	50 mg once daily	150 mg once daily
Telmisartan	40 mg once daily	80 mg once daily
<i>ARB and neprilysin inhibitor in combination</i>		
Sacubitril + valsartan	49/51 mg twice daily	97/103 mg twice daily

- Systolic blood pressure often falls to around 90–100 mmHg which does not prevent the continuation of treatment unless the patient experiences hypotension-induced symptoms, e.g. dizziness or reduced renal function.
- The monitoring of treatment response should include assessments of creatinine clearance (GFR), particularly in small-sized elderly women (calculator [1](#)).
- Diuretics sensitise the patient to the hypotensive effects of ACE inhibitors (and ARBs). In order to avoid hypotension at the start of treatment, reduction of the diuretic dose or even omitting a few doses merits consideration.
- Higher doses are usually tolerated during maintenance therapy, provided that the up-titration is carried out gradually. In most cases, dose increases every 2–4 weeks succeed without problems. In supervised situations (during in-patient care), dose increases may be introduced more quickly.
- If adverse effects (usually hypotension) make it impossible for the patient to tolerate high doses, even lower doses have been shown to be beneficial.
- Creatinine and potassium concentrations must be frequently monitored at the beginning of treatment; in severe HF the first check is indicated 4–7 days after treatment onset.
 - An increase of less than 20–30% in creatinine concentration is common and is not an indication to stop treatment.
 - If the creatinine concentration rises more than 50% from the baseline level, or the concentration exceeds 260 µmol/l (the limit should be set lower for elderly patients and small-sized women, i.e. < 160–200 µmol/l), the dose of the ACE inhibitor (or ARB) should be halved.
 - If the creatinine concentration continues to increase despite the dose reduction, the medication should be temporarily discontinued and other possible causes for the deteriorating renal function sought.
 - A marked rise in the creatinine concentration may in some cases signify renal artery stenosis.
 - Renal disease and potassium-sparing diuretics, spironolactone in particular, increase the risk of hyperkalaemia.
- Special indications for ACE inhibitors include valvular insufficiency and hypertension.
 - Severe valvular stenosis has traditionally been considered a contraindication.
 - However, most patients with aortic stenosis can tolerate an ACE inhibitor if the medication is started at a low dose and the patient is monitored for orthostatic symptoms.
 - The possibility of a corrective intervention on the aortic valve (either surgical or percutaneous) must, however, be initially considered in aortic stenosis.
- The most important adverse effects of ACE inhibitors are cough (10–20%), hypotension, hyperkalaemia and angio-oedema, which may occur even after several months of use.

- ARBs can be prescribed instead of ACE inhibitors, when a cough prevents the use of ACE inhibitors. Clinical studies have shown the efficacy of the ARBs candesartan and valsartan to be equal to that of ACE inhibitors in the treatment of systolic dysfunction.
- The combined use of ACE inhibitors, ARBs and mineralocorticoid receptor antagonists (spironolactone, eplerenone) is not recommended due to the risk of renal function impairment and possible development of hyperkalaemia.
- The combination of an ARB and a neprilysin blocker is a new drug. The experience on its wide-range use is very limited so far, as is the knowledge on its long-term effects. The treatment is started in specialized care.
 - The drug inhibits the effects of angiotensin by blocking the AT₁ receptor and the breakdown of endogenous natriuretic peptides mediated by neprilysin.
 - Since neprilysin also breaks down bradykinin, neprilysin inhibition also leads to an increase in bradykinin concentrations. This may increase the adverse effects related to bradykinin (cough, angio-oedema). In clinical trials (PARADIGM-HF) these effects have been minor and rarely a cause to discontinue treatment.

Beta-blockers [evd](#)

- Started for all patients with mild, moderate or severe systolic HF (NYHA II–IV), irrespective of aetiology.
- Asymptomatic left ventricular dysfunction after myocardial infarction is also an indication for beta-blockade.
- A beta-blocker is started with a small dose when the patient is clinically stable in combination with an ACE inhibitor (or ARB) and diuretic.
- Contraindications include bradycardia (heart rate < 50–60/min), hypotension (< 90 mmHg) and second or third degree AV block and, in some cases, severe asthma.
- Beta-blockers alleviate symptoms and improve long-term prognosis. They reduce the incidence of cardiac events, particularly those associated with arrhythmias. Patients with CHD or hypertension will gain most from beta-blockade.
- Dosage of beta-blockers: see table [7](#). The dose of a beta-blocker should be increased every few weeks whilst actively monitoring the patient's clinical condition.

Table 7. Dosage of beta-blockers (mg/day)

Beta-blocker	Test dose	Subsequent doses			Target
Bisoprolol	1.25 mg	2.5 mg	5 mg	10 mg	
Carvedilol	3.125 mg	6.25 mg	12.5 mg	50 mg	
Metoprolol succinate	12.5 mg	25 mg	50 mg	200 mg	
Nebivolol	1.25 mg	2.5 mg	5 mg	10 mg	

- Symptoms will improve slowly after 1–2 months. The HF symptoms may even worsen at the beginning of treatment, and it may be necessary to temporarily increase the dose of diuretics. If the HF symptoms continue to worsen despite the increased diuretic dose, a reduction of the beta-blocker dose should be considered (return to the last titration dose) and other possible causes for the deteriorating HF sought.
- Scientific evidence on the effect and on how to use beta-blockers in HF exists for metoprolol, bisoprolol, carvedilol and nebivolol.
- Beta-blocker induced adverse effects, such as bradycardia and AV node dysfunction, are more common in elderly patients (> 75–80 years).

Ivabradine

- Ivabradine slows the sinus rhythm by inhibiting the If channels of the sinoatrial node.
- Ivabradine has been investigated in patients with NYHA II–IV systolic HF. In the SHIFT study, ivabradine alleviated symptoms and reduced the need of hospital treatment better than placebo in patients with sinus rhythm when the heart rate was ≥70/min and LVEF ≤35% despite optimal standard treatment of HF (an ACE inhibitor or ARB together with a beta blocker and spironolactone).
- The drug does not slow ventricular response rate in AF.

- Ivabradine may be considered for patients who have stable systolic HF (NYHA II–IV) but for whom a beta blocker is unsuitable or who have a rapid sinus rate despite effective beta blockade.
- Initial dose is 5 mg × 2/day (for over 75-year-olds 2.5 mg × 2).
- The drug is not suitable for patients with a suspected sinoatrial node disease or an AV node block, or who have a resting heart rate of less than 60/min (before treatment start) or severe hypotension 90/50 mmHg.
- As adverse effects of ivabradine, abnormal luminous visual sensations (phosphenes) have been reported in 14.5% of patients. These refer to transient intensive increases of brightness in a limited area of the visual field. Phosphenes are usually mild or moderate and subside during the treatment.

Diuretics and spironolactone [evd](#)

- A diuretic should be combined with the other medication if fluid retention is present.
- Thiazides and furosemide inhibit the reabsorption of sodium chloride in the kidneys and thus increase the excretion of sodium and water. At the same time, they increase the excretion of potassium and magnesium and may therefore lead to hypokalaemia, hypomagnesaemia as well as to hypochloraemic alkalosis. Blood electrolytes should therefore be checked at the beginning of treatment and after each dose change.
- Treatment may commence with a thiazide if fluid retention is not excessive and the renal function is normal.
- Dosage of diuretics: see table [8](#).

Table 8. Starting and maintenance doses of diuretics (mg/day)

Diuretics	Starting dose	Usual maintenance dose
<i>Loop diuretic</i>		
Furosemide	20–40 mg	40–250 mg
<i>Thiazides</i>		
Hydrochlorothiazide	25 mg	50 mg
Indapamide	2.5 mg	2.5–5 mg
Metolazone	1.25 mg	2.5 mg
<i>Potassium-sparing diuretics *</i>		
Amiloride	2.5 mg	20 mg
Triamterene	25 mg	100 mg
Spironolactone	12.5 mg (25 mg**)	50 mg (100 mg**)
Eplerenone	12.5 mg	50 mg

* Dose when used with an ACE inhibitor/ARB (** dose if an ACE inhibitor/ARB is not in use)

- The maximum hydrochlorothiazide dose is 50 mg and it should normally not be exceeded. If a higher dose is needed, furosemide should be prescribed as it is more effective in renal failure (if creatinine > 180–200 µmol/l or creatinine clearance [GFR] < 30 ml/min).
- A thiazide and furosemide can be combined in severe fluid retention, if necessary.
- Spironolactone (or eplerenone) may also be added to the regimen if the patient has severe symptoms (NYHA III–IV) despite maximal treatment with an ACE inhibitor and beta-blocker.
 - Spironolactone is also a good choice in milder HF (NYHA II symptoms) if the patient is susceptible to hypokalaemia and needs potassium replacement.
 - The risk of hyperkalaemia is usually low if the dose of spironolactone does not exceed 25 mg/day.
 - Caution should be exercised if spironolactone is to be used in elderly patients or in renal failure. A daily dose of 12.5–25 mg is often sufficient. Potassium and creatinine should be checked 1–2 weeks after a dose change and regularly every 2–3 months.
 - The role of spironolactone in mild HF is not yet fully known.
- All diuretics slightly elevate creatinine and uric acid concentrations in the blood.
- A marked increase in the creatinine concentration may indicate too high a diuretic dose and dehydration.

- Signs of hypovolaemia include a fall in blood pressure, increased heart rate, collapsed neck veins and usually also an increased haematocrit and creatinine concentration.
- The patient may complain of abnormal fatigue and increased tendency to feel faint (orthostatism).
- When diuretics are started, the patient should be told about the possibility of diuretic-induced hyperuricaemia and gout, as well as about the preventative dietary regimen to be followed.
 - In the treatment of an acute attack of gout, anti-inflammatory drugs are indicated only for the management of severe symptoms.
 - If several attacks of gout occur within one year and the blood uric acid concentration is markedly increased, allopurinol should be started with a dose determined according to the patient's renal function.
- In severe HF, hyponatraemia is caused by fluid retention not by lack of salt. Sodium concentration may be around 130–135 mmol/l. Hyponatraemia can usually be corrected with fluid restriction. Adding salt to the diet will only increase fluid retention.
- *When HF is in a stable phase, the smallest diuretic dose required to prevent the development of fluid retention should be used.* However, the need for a diuretic changes greatly according to the severity of failure. The diuretic dose needed is affected by fluid intake and the amount of fluid loss from the body, e.g. through excessive sweating, vomiting or diarrhoea.
 - Regular weight monitoring, clinical assessment of the degree of oedema and dyspnoea are used to assess the diuretic dose needed.
 - The patient may be instructed to regularly monitor his/her weight, observe for oedema and to adjust the dose of the diuretic within preset limits.
- Cooperation with a nurse specialised in HF improves outcomes.
- More extensive re-evaluation of the HF treatment, hospital investigations and additional drug therapy, such as intravenous diuretics and inotropes, may be indicated if, despite the diuretic therapy, the patient's weight continues to increase, oedema worsens and dyspnoea persists (see Acute heart failure).

Digoxin evd

- Digoxin is used in patients with AF to slow a rapid ventricular response rate if a beta-blocker has not provided sufficient rate control.
- Digoxin may be used in sinus rhythm if severe symptoms (NYHA III–IV) persist, and other effective drug alternatives are already in use.
- Digoxin has no effect on survival but reduces the number of hospital admissions.
- Treatment doses should be kept small. A daily dose of 0.125 mg is commonly sufficient. In the elderly, small-sized patients and those with impaired renal function the dose may even be smaller, i.e. 0.0625 mg/day.
- Digoxin concentration in the blood should be checked early during treatment and whenever drug doses are changed and if renal impairment becomes evident. The target blood concentration is 0.5–0.9 ng/ml, which equals a molar concentration of approximately 0.6–1.1 nmol/l.
- Digoxin must not be started if the patient has second or third degree AV block, hypertrophic obstructive cardiomyopathy or WPW syndrome.
- The concentration and/or efficacy of digoxin may be potentiated in renal failure, hypokalaemia and by various medicinal products (e.g. amiodarone, quinidine, propafenone, calcium-channel blockers, spironolactone, erythromycin, omeprazole, tetracyclines, itraconazole).
- Signs of toxicity include: anorexia and nausea, confusion, headache and bradyarrhythmias. If toxicity is suspected the creatinine level must be checked as well as GFR and digoxin concentration. The risk of adverse effects increases if the concentration is > 0.9 ng/ml.

Anticoagulants and aspirin evd

- Anticoagulation with warfarin is indicated in patients with permanent or paroxysmal AF, an intracardiac thrombus detected by imaging or history of arterial embolism.
- Cardiomegaly and poor EF (< 30–35%) is associated with a risk of thromboembolism, but comprehensive studies on the benefit of anticoagulation in this patient group are lacking so far. When anticoagulation is considered, the patient's overall risk as regards both thromboembolic and bleeding complications must always be assessed.
- CHA₂DS₂-VASc and HAS-BLED scores are recommended for the assessment of thromboembolic and bleeding risks.

- Of the new oral anticoagulants, direct thrombin inhibitors and FXa inhibitors may come into question in dealing with the risk of thromboembolism associated with AF if warfarin therapy has not been successful and the patient does not have renal failure (GFR < 30 ml/min). The treatment should be individually pondered and negotiated with the patient.
- Aspirin is not as effective as warfarin. It may inhibit the beneficial effects of ACE inhibitors, and its routine use in HF is not justified. However, if the patient has CHD or other manifestations of atherosclerosis, aspirin should be prescribed with the dose of 75–100 mg/day.

Drugs to be avoided in HF [evd](#)

- A continuous use of NSAIDs
 - In renal disease, the use of NSAIDs should be totally withdrawn (they impair the effect of ACE inhibitors and ARBs as well as diuretics).
 - Coxibs: harmful effects are the same as with other anti-inflammatory drugs
- Systemic glucocorticoids (fluid retention)
- The calcium-channel blockers verapamil and diltiazem
- Antiarrhythmic drugs (possibility of proarrhythmia, negative inotropic effect)
- Antidiabetic drugs of the glitazone group (fluid retention)
- Tricyclic antidepressants (risk of proarrhythmia)
- Cytotoxic drugs with cardiotoxic effects (such as anthracyclines, trastuzumab)

Treatment of AF in HF

- Electrical cardioversion is recommended almost always for patients with new-onset AF, particularly if it is associated with rapid ventricular response not controlled by pharmacological measures.
- If AF has lasted for longer than 48 hours or its aetiology is unknown, the patient must first be anticoagulated and cardioversion carried out only after anticoagulation has been within the therapeutic target level (INR 2.0–3.0) for at least 3 weeks.
 - In urgent cases, cardioversion can be carried out earlier under LMWH cover, unless thrombus formation is detected in the atrial appendage or left ventricle (requires transoesophageal echocardiography).
- No comparative study data are available on the restoration and maintenance of sinus rhythm compared with rate control in AF in patients with HF.
 - The symptoms experienced by the patient during AF may guide decisions regarding treatment.
 - Some patients notice no difference in their symptoms whether they are in sinus rhythm or AF.
 - In some patients, the episodes of AF may quickly lead to the worsening of HF and even to pulmonary oedema. This might be the case particularly in diastolic HF, where ventricular filling is impaired due to the stiffening of the heart walls.
- In systolic HF, the only medication suitable for the maintenance of sinus rhythm is amiodarone since other antiarrhythmic agents (e.g. quinidine, disopyramide, flecainide, propafenone) may reduce the contractility of the left ventricle and increase mortality.
- Amiodarone therapy calls for regular monitoring of the patient for the emergence of adverse effects (thyroid, pulmonary, hepatic and nervous system dysfunction), and the daily doses should be kept as small as possible; usually 100–200 mg/day.
- In selected cases, catheter ablation may be considered to maintain sinus rhythm.
- If AF remains as the permanent rhythm, the heart rate usually needs to be slowed with a beta-blocker and, if necessary, digoxin. The aim is to have a heart rate of 60–100/min at rest.

Pacemaker therapy [evd](#)

- See
- The worsening of HF may in some cases be due to bradyarrhythmia, such as slow AF or AV block. The conventional indications for bradyarrhythmia treatment also apply to patients with HF.
- It is estimated that among patients with HF one in three have intraventricular conduction defects and dysynchronous myocardial contraction of the left ventricle.
 - The dysynchronous contraction may be corrected in some patients with pacemaker treatment whereby the left and right ventricles are paced with separate leads placed in situ via the right ventricle and coronary sinus (biventricular pacing, heart failure pacemaker).

- A heart failure pacemaker (also called cardiac resynchronisation therapy, CRT) can improve prognosis and alleviate symptoms in correctly selected patients.
- Patients in NYHA II–IV class who are symptomatic despite optimal medical therapy and whose ECG shows LBBB and QRS prolongation of ≥ 140 ms should be referred to a cardiologist for assessment regarding the possibility of pacemaker therapy. A heart failure pacemaker may also be considered in other types of intraventricular conduction disorders if the QRS complex is abnormally wide, ≥ 150 ms. The patient's suitability for pacemaker therapy is assessed with echocardiography.
- A patient who has been resuscitated from VF or who has been found to have life-threatening arrhythmias during rhythm monitoring (ambulatory Holter monitoring or telemetry on a hospital ward) should be referred to an electrophysiologist for assessment regarding the need for an implantable cardioverter defibrillator (ICD).
 - Devices that provide both biventricular pacing and defibrillator function (CRT-D = cardiac resynchronisation therapy-defibrillator) are now available for patients with HF.

Treatment of HF in the elderly

- Elderly patients often have several comorbidities and drug therapies which hinder the realisation of HF therapy and cause interactions.
 - The most common of these are renal failure, COPD, type 2 diabetes, anaemia and joint complaints requiring the use of NSAIDs.
- It may not be possible to implement all medications that are known to improve prognosis with the dosages recommended in clinical guidelines. The treatment is often mainly symptomatic.
- Even a small increase in the creatinine concentration in a small-sized elderly patient may signify markedly impaired renal function, for example a creatinine level of 120–130 $\mu\text{mol/l}$ may echo a GFR value of < 30 ml/min (calculator [1](#)).
- ACE inhibitors (ARBs) are more likely to cause hyperkalaemia and impaired renal function in the elderly.
- It is more likely that digoxin levels exceed the therapeutic range, and the risk of arrhythmias and conduction defects increases.
- Beta-blockers may induce conduction defects.
- Nitrates and other vasodilating drugs increase the risk of falls in elderly patients who use multiple medications.
- An elderly patient will often need pain relief. Self-care using anti-inflammatory drugs may further impair renal function and cause fluid retention as well as increase the number of cardiovascular complications.
- See also chapter Precipitating and exacerbating factors of HF.

Management of worsening HF or treatment-resistant HF

- A variety of factors may be behind a poor treatment response in HF.
 - Pharmacological therapy has not been increased up to doses that have been proven effective in studies.
 - The patient may have developed new diseases or there may be new treatments that weaken the efficacy of HF treatment.
 - There may also often be in the background problems associated with the implementation of treatment for a variety of reasons (see also chapter Precipitating and exacerbating factors of HF).
 - A diagnosis based purely on clinical signs may be wrong, the mechanism of HF may have changed or it has not been fully understood.
- If no clear and easily treatable cause for the worsening HF can be identified, the patient should be admitted to hospital for appropriate management (see also Acute heart failure).
- Fluid retention may initially need treatment with intravenous diuretics (i.v. furosemide).
- If, however, HF has deteriorated due to too effective diuretic therapy and consequent dehydration, careful rehydration may be the treatment of choice.
 - In such a case, it may also be necessary to include inotropic medication to the regimen (see Acute heart failure).

Patient education and self-care [evd](#)

- Involving the patient in the treatment and self-care measures can help bring the condition under control and detect symptoms of deterioration. Well implemented self-care can reduce the need for hospitalisation and improve prognosis.
- The patient can be advised to monitor his condition for the following symptoms:
 - the occurrence of exertional dyspnoea (what type of exercise brings it on?)
 - dyspnoea when lying down or at night, nocturnal cough
 - weight in the morning before breakfast
 - abdominal pains, abdominal bloating, appetite.
- The patient should be given written basic information about all his/her diseases and the drug therapies to treat them as well as information about aggravating factors and stays in hospital.
- An action plan should be devised about what to do should the condition worsen or if signs of dehydration occur.
- The patient may be advised on how to adjust the dose of a diuretic (furosemide) within preset limits, for example: a weight gain of 1–2 kg within a few days may require an additional 20 mg dose of furosemide. However, if the weight gain continues, the treatment regimen should usually be urgently reassessed.
 - In severe HF, fluid restriction is needed in addition to the diuretic therapy. This may, however, be difficult to manage at home, and it is rarely possible for the patient to restrict his/her fluid intake to 1.5–2.0 l/day.
- Various pill boxes and organisers are available and may be used to facilitate the implementation of therapy that consists of several different medicines.

Follow-up [evd](#)

- Frequent follow-up visits, every 2–4 weeks, are indicated at the beginning when the diagnosis is new and also in severe or unstable HF. The severity of HF and the patient's symptoms determine the frequency of further visits. Some of the follow-up visits can be carried out by a specially trained nurse or via telephone.
- During the follow-up visits, the patient should be asked about his/her symptoms, exercise capacity and weight changes. If there is conflict between the symptoms described by the patient and the clinical findings, proBNP or BNP determination may be indicated.
- It is advisable that at least the following are checked at a routine follow-up visit: basic blood count with platelet count, plasma sodium, potassium, creatinine and glucose, and ECG. The INR should be checked in patients using warfarin. Iron deficiency should be detected and the efficacy of iron therapy monitored by determining ferritin and transferritin receptor (TfR) concentrations. The concentration of digoxin in the blood should be checked if the dose has been changed, renal function has deteriorated or new medicines that affect digoxin concentrations have been started (see Digoxin [2](#)).
- A cardiologist consultation and echocardiography are indicated if the aetiology of HF is unclear or if the treatment response is worse than expected.
- When drug therapy is started, the doses are usually small, and they should be regularly monitored and adjusted according to the patient's condition. In most cases, it is possible to gradually increase the dose of an ACE inhibitor (ARB) and a beta-blocker a few weeks (one month) after hospital discharge. If the treatment progresses well, the diuretic dose can usually be reduced.
- Cooperation between the specialist care and primary care is important, particularly for patients with severe HF. Fast information flow regarding the medication and the treatment actions should be guaranteed for all the care settings involved and for the patient.

End-of-life treatment

- If the symptoms caused by HF remain severe despite the most effective treatment possible, and curative or symptom-relieving procedures cannot be performed, the treatment should be focussed on providing the best possible palliative treatment.
 - The principles described in the article Palliative treatment of cancer can be applied.
- The basic drug therapy for HF (diuretics, heart rate controlling medication) should not be discontinued since it usually also effectively alleviates the symptoms.
- Taking care of basic needs, alleviating thirst
- Anxiety- and pain-relieving medication (opioids)

- If the patient has an implantable cardioverter defibrillator, deactivating it should be discussed with the patient.

Related resources

- Cochrane reviews [1](#)
- Other evidence summaries [1](#) [evd](#)
- Clinical guidelines [1](#)
- Literature [1](#)

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