

PART 2 | WHAT DO YOU KNOW ABOUT

The pharmacologic management of heart failure and its co-morbidities: what is written in the guidelines?

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Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) caused by a structural and/or functional cardiac abnormality; ischemic heart disease is the commonest cause. Approximately 1–2% of the adult population in developed countries suffer from heart failure, rising to $\geq 10\%$ among people 70 years of age. Clinically, it is divided according to the NYHA functional classification into four severity levels. Based on ejection fraction (EF), heart failure is divided into HF with preserved ejection fraction (HFpEF) when $EF \geq 50\%$, HF with reduced EF (HFrEF) when $EF < 40\%$, and HF with a middle range EF (HFmrEF) when EF is in the range of 40–49%. This classification is of importance in terms of epidemiology, management, and prognosis. In this educational source, we are presenting important messages about the drug therapy of heart failure with treatment of some co-morbidities based on the latest ESC and AHA guidelines.

Questions

Q 1: Biomarkers screen in prevention of heart failure

A 55-year-old male patient presented to the outpatient department for checkup. He was hypertensive and diabetic for the last ten years on *lisinopril* 10 mg/day and *metformin* 1000 mg/day, asymptomatic for the time being. On clinical exam blood pressure is 145/90 mmHg and his HbA1c is 7%.

Which of the following statement is the most appropriate next step true?

- a) Give dietary advice and schedule for next visit.
- b) Increase the dose of *lisinopril* to 20 mg/day and *metformin* to 2000 mg/day.
- c) Add *statin* and *antiplatelet* to his medication.
- d) Ask for brain natriuretic peptide screen (BNP) and optimise guidelines directed management and therapy (GDMT).
- e) Being asymptomatic, no further action is needed.

Q 2: Drugs affect survival of patients with heart failure

All the following drugs improve survival in patients with HFrEF except:

- a) Beta blockers
- b) ACE inhibitors
- c) Loop diuretics
- d) Sacubitril
- e) Spironolactone

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Q 3: Role of ARNI in patient with HFrEF

A 65-year-old female diagnosed as heart failure due to uncontrolled hypertension for many years asked your opinion about her medical therapy. She is a house wife doing most of her usual daily activities, during the last three months she noticed that her exercise capacity became more limited and now she gets tired with SOB for even going to bathroom. On clinical exam: BP 130/80 mmHg, HR 60 bpm regular with normal volume, JVP normal, normal cardiac auscultation, clear lung bases and no pedal oedema. Her current treatment includes: *ramipril* 5 mg/day, *indapamide* 1.5 mg/day, *carvedilol* 25 mg/day, *spironolactone* 25 mg/day. ECG showed LVH, Echocardiography showed EF 40%.

What will be the most appropriate step:

- Increase the dose of *ramipril* to 10 mg / day.
- Increase *spironolactone* to 50 mg /day.
- Replace *ramipril* by *valsartan/sacubitril* therapy.
- Start *torsemide* tab 10 mg /day
- Increase *carvedilol* to 50 mg /day.

Q 4: Drugs not indicated or harmful in heart failure

All these statements are false regarding drug therapy of HFrEF Except:

- ARBs are more effective than ACE inhibitors.
- To prevent the potential risk of thrombosis all patients should be kept on anticoagulation.
- Verapamil and *diltiazem* can be used safely in those patients to treat high blood pressure.
- Aspirin* is not indicated for patient with HFrEF unless in the presence of CAD.
- There is a growing role for statin in the treatment of patient with HFrEF.

Q 5: Indication for Ivabradine in heart failure

All of the following statement related to Ivabradine usage to reduce heart failure hospitalization are true Except:

- Maximum tolerated doses of GDMT beta blocker therapy should be in place before starting Ivabradine.
- NYHA class II-III.
- EF less than 35%.
- Should be in sinus rhythm .
- Heart rate should be less than 70 bpm.

Q 6: Iron deficiency anaemia in heart failure

During assessment of patient with heart failure ,the base line screen showed : Hb 10 mg/dl, blood urea 20 mg/dl, serum creatinine 0.9 mg /dl serum ferritin 30 ng/ml (normal value is 20-250 ng/ml for males and 10-120 ng/ml for females), the next step should be:

- Oral iron therapy as it showed improvement in quality of life (QoL).
- Parenteral iron therapy as it shoed improvement in QoL.
- Advice for iron rich diet only.
- Add oral multivitamin rich in iron.
- Subcutaneous erythropoietin stimulating agent.

Q 7: Hypertension in heart failure

A 55-year-old patient, presented to outpatient clinic because of being told that he was hypertensive. His mother died at the age of 50 years because of heart failure and his younger brother is hypertensive, he is currently heavy smoker and his fasting lipid profile showed total cholesterol of 320 mg/dl. On clinical exam his BP was 160/100 mmHg, the rest of exam was normal.

Which of the following statement related to BP target (office reading) that help in heart failure prevention is true ?

- a) BP target should be below 150/100 mm Hg
- b) BP target should be below 140/95 mm Hg
- c) BP target should be below 130/90 mm Hg
- d) BP target should be below 130/80 mm Hg
- e) BP target should be below 120/70 mm Hg

Q 8: Sleep disorder and heart failure

Sleep disorders are common in patients with heart failure, it was found that 61% of patients with heart failure had some sort of sleep disorder (central or obstructive sleep apnea) and therefore a formal sleep study should be conducted on suspicion.

Which of the following statement is true?

- a) In obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness.
- b) In obstructive sleep apnea, CPAP may be reasonable to improve survival.
- c) In patients with NYHA class II–IV HFrEF and central sleep apnea, adaptive servo-ventilation is appropriate therapy
- d) The management for both obstructive and central sleep apnea (CSA) is the same

Q 9: Diuretic therapy in patient with heart failure

A 60 year old patient who had been previously diagnosed as ischemic heart disease and heart failure, presented to the emergency department complaining from fatigue, SOB and orthopnoea but no chest pain.

On clinical exam: Looks tired, anxious and in respiratory distress, couldn't lie flat, BP 110/80 mmHg, pulse 110 bpm normal volume, O2 sat 90% at room air, JVP 8cm above costal margin, cold extremities, soft S1 S2 and S3 gallop, no murmurs, bilateral basal crepitation. His current medication was: oral furosemide 80 mg/day, Enalapril 10 mg/day, spironolactone 25 mg/day, isosorbide dinitrate 20 mg /d day and carvedilol 25 m/d day.

Your decision was to admit the patient and start parenteral diuretic therapy, which of the following statement is true as regard to the initial dose?

- a) Start intravenous furosemide 40 mg twice daily
- b) Start intravenous furosemide 60 mg twice daily
- c) Start intravenous furosemide 80 mg twice daily
- d) Start intravenous furosemide 100 mg twice daily

Q 10: Management of patients with HFpEF

A 65-year-old lady who is known to be hypertensive and diabetic for the last 15 years consulted you because of progressive exercise intolerance and shortness of breath for the last six months. During the last week she started to have SOB on lying down and bilateral pedal oedema but there was no chest pain or palpitation and she was kept on *atenolol* 100 mg/day, *Glucophage* 1500 mg/day.

On clinical exam: BMI 28 kg/m², BP 160/105 mmHg, pulse 88 bpm, JVP 8 cm above sternal margin, normal S1, loud S2, S4, no murmur, few bilateral basal lung crepitation and ++ bilateral pedal oedema. Full laboratory testing was normal apart from HbA1c 8%, Pro BNP 80.0 pg/ml, and triglyceride 300 mg/dl. Echocardiography showed LV EF of 62%.

Which of the following statement related to this patient management is true?

- Heart failure is unlikely in this patient and we should look for alternative cause.
- Controlling both systolic and diastolic BP is priority in this patient management.
- Calcium channel blockers is the 1st line therapy to control this patient hypertension.
- Diuretics is of limited value in the management of this lady.
- Nutritional supplements is usually useful in this patient management.



Abbreviations list: American Heart Association (AHA), Angiotensin converting enzyme inhibitors (ACEI), Angiotensin receptor blockers (ARBs), Angiotensin receptor neprilysin inhibitor (ARNI), Beat per minute (bpm), Blood pressure (BP), Body mass index (BMI), Brain natriuretic peptide screen (BNP), Calcium channel blockers (CCBs), Central sleep apnea (CSA), Class of recommendation (COR), Continuous positive airway pressure (CPAP), Coronary artery disease (CAD), Cyclo-oxygenase 2 inhibitors (COX2 inhibitors), Ejection fraction (EF), Electrocardiography (ECG), European Society of Cardiology (ESC), Guidelines directed management and therapy (GDMT), Heart failure (HF), Heart rate (HR), HF with a middle range EF (HFmrEF), HF with preserved Ejection fraction (HFpEF), HF with reduced EF (HFrEF), Intravenous (IV), Jugular venous pressure (JVP), Left ventricular hypertrophy (LVH), Level of evidence (LOE), Mineralocorticoid receptor antagonist (MRA), New York Heart Association (NYHA), Non-steroidal anti-inflammatory drugs (NSAIDs), Obstructive sleep apnoea (OSA), Quality of life (QoL), Shortness of breath (SOB), Sleep-disordered breathing (SDB).

Explanation of classes of recommendation and level of evidence used in the answers of these questions

Class (strength) of recommendation (COR)		
	Class I	(Strong) Benefit >>> Risk. The intervention is recommended/ indicated/ useful/ effective.
	Class IIa	(Moderate) Benefit >> Risk. The intervention is reasonable
	Class IIb	(Weak) Benefit ≥ Risk. The intervention may be reasonable
	Class III	No benefit (moderate) Benefit = Risk. The intervention is not recommended
	Class III	Harm (Strong) Risk > Benefit. The intervention is potentially harmful
Level (Quality) of evidence (LOE)		
	Level A	High quality evidence of more than one RCT, or meta-analysis of such studies.
	Level B-R	Moderate quality evidence RCT or meta-analysis (Randomized)
	Level B-NR	Moderate quality non-randomized or observational studies. Or meta-analysis on such studies.
	Level C-LD	Limited data. R and non-R CT of limited design or their meta-analysis.
	Level C-EO	Expert opinion

Answers

Q 1: The correct answer is d

In addition to its useful role in supporting or excluding the diagnosis of heart failure, for patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing guidelines directed management and therapy (GDMT) to address the risk factors, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF. Elevation of natriuretic peptide should be interpreted cautiously, because many cardiac and noncardiac conditions can increase it as well. Obesity may be associated with lower natriuretic peptide concentrations, and this may modestly reduce diagnostic sensitivity in morbidly obese patients. **Table 1** shows these conditions

New data suggest that natriuretic peptide biomarker screening and early intervention to control risk factor may prevent HF.

Table 1 Potential Causes of Elevated Natriuretic Peptide

Cardiac
HF, including RV syndromes
Acute coronary syndromes
Heart muscles disease, including LVH
Valvular heart disease
Pericardial disease
Atrial fibrillation
Myocarditis
Cardiac surgery
Cardioversion
Toxic-metabolic myocardial insults, including cancer chemotherapy
Noncardiac
Advancing age
Anaemia
Renal failure
Pulmonary: obstructive sleep apnea, severe pneumonia
Pulmonary hypertension
Critical illness
Bacterial sepsis
Severe burns

COR	LOE
Ia	B-R

Q 2: The correct answer is c

Neuro-hormonal antagonists [ACEIs, MRAs (mineralocorticoid receptor antagonist) and beta-blockers] have been shown to reduce hospitalization and death in patients with HFrEF and are recommended for the treatment of every patient with HFrEF, unless contraindicated or not tolerated. Angiotensin receptor neprilysin inhibitor (ARNI) like Sacubitril reduces the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA. Diuretics including loop diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion but not to change survival.

ACE inhibitors, beta blockers and Potassium-sparing diuretics should be used in every patient with HFrEF unless contraindicated or not tolerated.

ACEI, ARBs	I	A
ARNI	I	B-R
Beta blockers, MRA	I	A*

* ESC guidelines 2016/ acute and chronic heart failure.

Q 3: The correct answer is c

Neprilysin is an enzyme that degrades natriuretic peptides, bradykinin and other vasoactive peptides. Neprilysin inhibitor combined with an ARB (ARNI) reduces the CV mortality or HF hospitalization significantly in persistently symptomatic patient with HFrEF NYHA class II or III who is using ACEI.

ACE inhibitors, beta blockers and Potassium-sparing diuretics should be used in every patient with HFrEF unless contraindicated or not tolerated.

COR	LOE
I	B-R



Q 4: The correct answer is d

Verapamil / Diltiazem	III*	A
NSAIDs/ COX2 inhibitors	III*	B

* ESC guidelines 2016/ acute and chronic heart failure.

ARBs are recommended only as an alternative in patients intolerant of an ACEI. Anticoagulants are not used routinely in patients with HFrEF unless it is indicated for prevention of thrombosis like in atrial fibrillation or treatment of already existed thromboembolic disease for example pulmonary embolism. (CCBs) are not indicated for the treatment of patients with HFrEF. *Diltiazem* and *verapamil* have been shown to be unsafe in patients with HFrEF. There is only evidence on safety for *amlodipine* and *felodipine* in patients with HFrEF, and they can be used only if there is a compelling indication in patients with HFrEF. Although statins reduce mortality and morbidity in patients with atherosclerotic disease, they are not effective in improving the prognosis in patients with HFrEF.



Statins, antiplatelets, and anticoagulants are not routinely used unless indicated for another reason, while verapamil and diltiazem are harmful.



Q 5: The correct answer is e

COR	LOE
Ila	B-R

Ivabradine slows the heart rate through inhibition of the I_f channel in the sinus node and therefore should only be used for patients in sinus rhythm. It can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF < 35%) who are receiving guidelines directed management and therapy (GDEM), including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.



In HFrEF, *Ivabradine* therapy reduces hospitalization.



Q 6: The correct answer is d

COR	LOE
Iib	B-R

In patients with NYHA class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation is < 20%), intravenous iron replacement might be reasonable to improve functional status and QoL. Routine baseline assessment of all patients with HF includes an evaluation for anaemia in addition to other baseline laboratory measurements. Anaemia is independently associated with severity of HF disease, and iron deficiency appears to be uniquely associated with reduced exercise capacity. When iron deficiency is diagnosed and after full evaluation for cause, intravenous repletion of iron, may improve exercise capacity and QoL.



Proper treatment of Iron deficiency anaemia improves functional status and QoL in patient with heart failure.



Q 7: The correct answer is d

COR	LOE
I	B-R

In patients at increased risk, stage A HF, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg. Patients with HFrEF and HFpEF and hypertension should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mmHg.



Blood pressure target for primary prevention of heart failure should be < 130/80 mmHg.

Q 8: The correct answer is a

Perform sleep study	Ila	C-LD
Use of CPAP	Iib	B-R
Servo-ventilation for CSA	III	B-R

Sleep-disordered breathing (SDB) occurs in about 60 % of patients with HF. The commonest are obstructive sleep apnoea (OSA) and central sleep apnoea (CSA). CSA and OSA have been shown to be associated with a worse prognosis in HF. OSA is associated with an increased risk of incident HF in men. In patients with NYHA class II–IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable. If OSA is diagnosed, CPAP may be reasonable to improve sleep quality and daytime sleepiness. In patients with NYHA class II–IV HF and central sleep apnea, use of adaptive servo-ventilation led to an increase in both all-cause and cardiovascular mortality.



Sleep study is indicated for patients with HF if there is suspicion of sleep disturbance or daytime somnolence.

Q 9: The correct answer is d

For example, for patients taking 40 mg of oral furosemide twice daily as an outpatient, initial intravenous (IV) dosing would be 100 mg of furosemide IV twice daily. For patients not receiving long-term loop diuretics agents, 40–80 mg IV BID of furosemide or the equivalent is a reasonable empiric starting dose. Due to post-dosing Na⁺ retention, IV loop diuretic agents should usually be given at least twice daily.



For patients with heart failure on long-term loop diuretic agents who were admitted to hospital after decompensation, 2.5 times their outpatient dose on a mg per mg basis, demonstrated safety and efficacy in the DOSE trial.

Q 9: The correct answer is b

Diuretics for volume overload	I	B
ACEI, B Blockers, ARBs	Ila	C

Blood pressure control in accordance with hypertension guidelines remains the most important recommendation in patients with HFpEF. Evidence from a randomised controlled trials has shown that improved blood pressure control reduces hospitalization for HF, decreases cardiovascular events, and reduces HF mortality in patients without prevalent HF. In hypertensive patients with HFpEF, aggressive treatment (often with several drugs with complementary mechanisms of action) is recommended. Diuretics should be used for relief of symptoms due to volume overload in patients with HFpEF. The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF.



Most of the recommended therapies for patients with HFpEF are directed at symptoms, especially comorbidities, and risk factors that may worsen cardiovascular disease.

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