Practical approaches for the treatment of chronic heart failure: Frequently asked questions, overlooked points and controversial issues in current clinical practice

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Abstract

Heart failure (HF) is a progressive disorder associated with impaired quality of life, high morbidity, mortality and frequent hospitalization and affects millions of people from all around the world. Despite further improvements in HF therapy, mortality and morbidity remains to be very high. The life-long treatment, frequent hospitalization, and sophisticated and very expensive device therapies for HF also leads a substantial economic burden on the health care system. Therefore, implementation of evidence-based guideline-recommended therapy is very important to overcome its worse clinical outcomes. However, HF therapy is a long process that has many drawbacks and sometimes HF guidelines cannot answers to every question which rises in everyday clinical practice. In this paper, commonly encountered questions, overlooked points, controversial issues, management strategies in grey zone and problems arising during follow up of a HF patient in real life clinical practice have been addressed in the form of expert opinions based on the available data in the literature. *(Anatol J Cardiol 2015: 15 Suppl 2; 1-60)*
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1.0 Introduction – Lale Tokgözoğlu

Heart failure (HF) is one of the most common causes of mortality and hospitalizations in adults and is gradually becoming a global epidemic. Currently, approximately 26 million adults live with HF in the world. It is estimated that this number will increase substantially with aging populations. Even though the prevalence is not clearly known in our country, absolute HF prevalence in adults was found to be 2.9% in the HAPPY Study (1) which is higher than Western countries. 85% of HF patients in the U.S. and Europe are 65 years of age or over. The average age of HF in our country is lower than that of Europe (2). It is estimated that these numbers will rise with our aging population.

Heart failure causes major costs to the healthcare economy owing to life-long treatment, frequent hospitalization, and sophisticated and very expensive device therapies. Almost 1-3% of total healthcare costs are spent for the management of HF in Western Europe.

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Heart failure is a progressive and irreversible disorder. Therefore, prevention of HF is of great importance. Primarily, it is required to control the risk factors of HF and the leading underlying causes. If the disease has settled in, it is important to implement the guidelines recommended therapy. Inadequate treatment or incompliance with treatment increases mortality. Almost 17-45% of hospitalized HF patients die within one year. It is possible to increase survival with compliance to guideline recommendations and the right treatment. In these patients, treatment is a long process that has many difficulties. The guidelines sometimes cannot answers to every question which rises in everyday clinical practice regarding problems, controversial issues and managing complications. In this grey zone, clinical experience comes into prominence in decision-making.

In this paper, we aimed to adress controversial issues, commonly encountered questions, overlooked points, new drugs, management strategies in grey zone and problems arising during follow up of a HF patient in real life clinical practice in the form of expert opinions based on the available data in the literature.

2.0 What are the targets of therapy in heart failure? – Yüksel Çavuşoğlu

Basic treatment targets in chronic HF are reducing mortality and re-hospitalization, relieving symptoms and signs, increasing functional capacity and improving quality of life (3, 4). In most of the major HF trials, all-cause mortality, mortality from HF, cardiovascular mortality and sudden deaths are targeted as primary and secondary mortality outcomes. Similarly, in these major HF trials, in addition to HF re-hospitalization, cardiovascular hospitalization and all-cause hospitalizations were investigated. Although symptom control, functional capacity and quality of life have been evaluated as secondary endpoints in many studies, they are referred as basic treatment targets in the follow-up of these cases. In addition to these basic targets, slowing, stopping or reversing disease progression, controlling congestion, reducing the levels of natriuretic peptide levels, increasing peak oxygen consumption, providing an increase in a 6-min walk distance, providing a decrease in left ventricular systolic and diastolic volumes, reducing the emergency service and hospital admissions are among the targets to be achieved in clinical follow-up (Table 1).

3.0 General recommendations – Mehdi Zoghi

3.1 Is salt restriction necessary? If so, how much?

There is no strong evidence regarding the benefit of salt restriction in HF based on randomized, controlled trials. There are studies showing that salt restriction is necessary (5), however, there is also data showing that it has no benefit. It is suggested that a salt-free diet may cause neurohormonal activation in HF. A normal salt diet has not been shown to be harmful. However, it is generally accepted that excess sodium intake increases hospitalization by causing fluid retention in the body.

In a meta-analysis in which six randomized trials were evaluated, very low-sodium diet (1.8 gr/day) was reported to increase the rate of all-cause mortality (RR 1.95, 1.66 vs. 2.29) and hospitalization (RR 2.10, 1.67 vs. 2.64). Even though studies in this aspect mainly include patients with systolic HF, there are also observational studies reporting favorable effects of DASH diet on diastolic functions in hypertensive patients who have HF with preserved ejection fraction (6).

There is data showing that in patients presenting with acute decompensated HF, fluid (maximum 800 mL/day) and sodium (maximum 800 mg/day) restriction has no effect on weight-loss or clinical improvement (7). Acute HF is a clinical syndrome in which various neurohormonal and triggering factors are involved in the pathophysiology and salt restriction should not be generalized in all groups in acute HF.

Clinical effect of sodium amount in diet in HF shows a U-shape curve effect (excess consuming and excess restriction are harmful) rather than linear relationship (8). A low salt diet is represented by daily sodium consumption of 2-3 grams (1-2 flat teaspoon of salt). HF guidelines recommend that HF patients consume less salt than the normal population (Table 2). Recommendations for the daily amount of sodium consumption vary depending on the type of HF (systolic or diastolic), accompanying diseases, New York Heart Association (NYHA) functional class and severity of the disease (3). In patients with systemic congestion, salt restriction is strongly recommended.

The American Heart Association restricts daily sodium intake with 1.5 gr/day in asymptomatic stage A and B HF patients in which hypertension and cardiovascular disease usually play a role in etiology. In symptomatic stage C and D HF patients, daily sodium intake is recommended to be <3 gr/day (4). Guidelines recommendations for daily sodium restriction are shown in Table 2.

Table 1. Targets of therapy in heart failure

Basic targets
Controlling symptoms and signs
Reducing mortality
Reducing re-hospitalization
Increasing functional capacity
Improving quality of life
Clinical targets
Slowing, stopping or reversing disease progression
Controlling congestion
Decreasing natriuretic peptide levels
Increasing peak oxygen consumption
Providing an increase in a 6-min walk distance
Providing a decrease in systolic/diastolic ventricle volumes

Table 2. Guidelines recommendations for daily sodium restriction

2013 ACCF/AHA	<3 gr/day
HFSA 2010	2 gr/day
AHA General	<1.4 gr/day
Canadian Cardiovascular Society HF 2012	No recommendation
ESC-HFA 2012	May be beneficial in NYHA Class III and IV patients

ACCF – American College of Cardiology Foundation; AHA – American Heart Association; HFSA – Heart Failure Society of America; HF – Heart failure; ESC – European Society of Cardiology, HFA – Heart Failure Association

3.2 Daily weight monitoring: How should it be performed?

In HF patients, ensuring and preserving dry body weight are essential in the management of clinical course of the disorder. Weight gain due to fluid overload has a special clinical importance in terms of gradual worsening of symptoms and frequent hospitalization. Weight gain is known to increase the risk of hospitalization by 2.77 fold. Therefore, in the course of HF treatment, daily weight monitoring (in the morning, after going to the toilet, at the same morning hour and with the same weighing scale) should be performed; and in patients who have weight gain more than 2 kg in 3 days, the diuretic dose should be increased and/or they should refer to their doctor. Well-educated patients with good treatment compliance can maintain their dry body weight by increasing and decreasing the diuretic doses according to their daily weight monitoring. In HF patients monitoring their daily weight regularly, annual hospitalization was shown to have decreased significantly (9-11).

3.3 Should fluid restriction be performed?

There is no data regarding the clinical benefit of routine fluid restriction in all patients with HF. Therefore, it is generally accepted that there is no need for fluid restriction, except for Stage D HF patients, particularly, with hyponatremia, refractory congestion or diuretic resistance. In patients in whom fluid restriction is considered, daily fluid intake is generally restricted to 1.5 L/day. However, in patients with hypervolemic hyponatremia, daily fluid intake can be restricted up to 0.5-1 L/day. It is also reported that fluid restriction performed based on the body weight (30 ml/kg/day in patients <85 kg and 35 ml/kg/day in patients >85 kg) can prevent the development of thirst sensation (3, 4).

3.4 Regular exercise training programs: How should they be performed?

Regular exercise training programs for 30 minutes a day and 5 days in a week accompanied by optimal medical therapy have favorable effects on HF-related symptoms and survival. In the HF-ACTION trial, it was reported that an 11% decrease in all-cause mortality or hospitalization and a 15% decrease in cardiovascular death or HF hospitalization were observed in patients who were on aerobic exercise training program 5 days a week. Cardiac rehabilitation programs implemented in clinically stable patients improve NYHA functional capacity, exercise duration and quality of life as well as mortality (4, 12).

4.0 Evidence-based drug therapy – Sanem Nalbantgil, Yüksel Çavuşoğlu

4.1 What should the basic drugs and treatment algorithm be?

Drugs that are used in the treatment of HF with reduced ejection fraction (HF-REF), the efficacy of which has been proven, are angiotensin converting enzyme inhibitors (ACEIs)/ARBs, BBs, mineralocorticoid receptor antagonists (MRA), ivabradine, diuretics, hydralazine and isosorbide dinitrate (H-ISDN) combination and digoxin (Table 3). It is expected that angiotensin receptor neprilysin inhibitors (ARNI) will replace ACEIs in the near future, based on the strong evidence in reducing mortality and re-hospitalization compared to ACEIs.

Angiotensin converting enzyme inhibitors and BBs are drugs that have been proven to definitely reduce the mortality and morbidity rates in patients with systolic HF, regardless of HF etiology. ARBs are recommended as an alternative in patients who have contraindication or intolerance to ACEIs. MRAs, added to the ACEI and BB treatments, reduce mortality and hospitalization further in patients with NYHA Class II-IV HF. Even though there is no evidence showing that they decrease mortality, diuretics are basic agents that are used in the treatment of symptomatic cases with systemic and pulmonary congestion. Adding MRA to the treatment is recommended in patients having uncontrolled symptoms despite optimal ACEI and BB treatments. It has been shown that adding ivabradine to the treatment in patients with ongoing symptoms who are in sinus rhythm with a heart rate

Table 3. Basic drugs in HF-REF

ACEI* (ARBs)*†
Beta blockers*
MRAs*
Ivabradine*
Hydralazine+isosorbide dinitrate*
Diuretics
Digoxin
ARNIs*

*Proven to have decreased mortality in randomized clinical trials
†ACEIs are the first choice. ARBs are recommended in the case of ACEI inhibitor intolerance
ACEIs – angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers; ARNIs – angiotensin receptor neprilysin inhibitors; HF-REF – heart failure with preserved ejection fraction; MRAs – mineralocorticoid receptor antagonists

of ≥70 b.p.m reduced cardiovascular mortality or, in particular, re-hospitalization. In patients who are still symptomatic, adding H-ISDN combination to the treatment is known to provide benefit, particularly in African-Americans. Digoxin which has been shown to have no beneficial effect on mortality is used in the treatment of HF, mainly in patients with atrial fibrillation (AF), with the goal of reducing hospitalizations, relieving symptoms and improving quality of life (Figure 1). ACEIs/ARBs, BBs and MRAs, which have been proven to decrease mortality in HF with reduced ejection fraction, are recommended as Class I indication by the guidelines (3, 4). It has been shown that all these three groups of drugs relieve symptoms and improve quality of life, reduce re-hospitalizations, delay, prevent or reverse the progression of left ventricle systolic dysfunction. In patients who have intolerance or contraindication to ACEIs/ARBs, H-ISDN is recommended as an alternative. Also, in patients who have intolerance or contraindication to BBs, ivabradine or digoxin can be used as an alternative therapy. In this case, choice of ivabradine in patients with elevated heart rate and in sinus rhythm and digoxin in patients with normal heart rate or AF seems to be reasonable.

4.2 Which drugs are effective in reducing mortality?

In patients with HF with reduced ejection fraction (HF-REF), ACEIs or ARBs, beta-blockers (BBs) and MRAs have been prov-

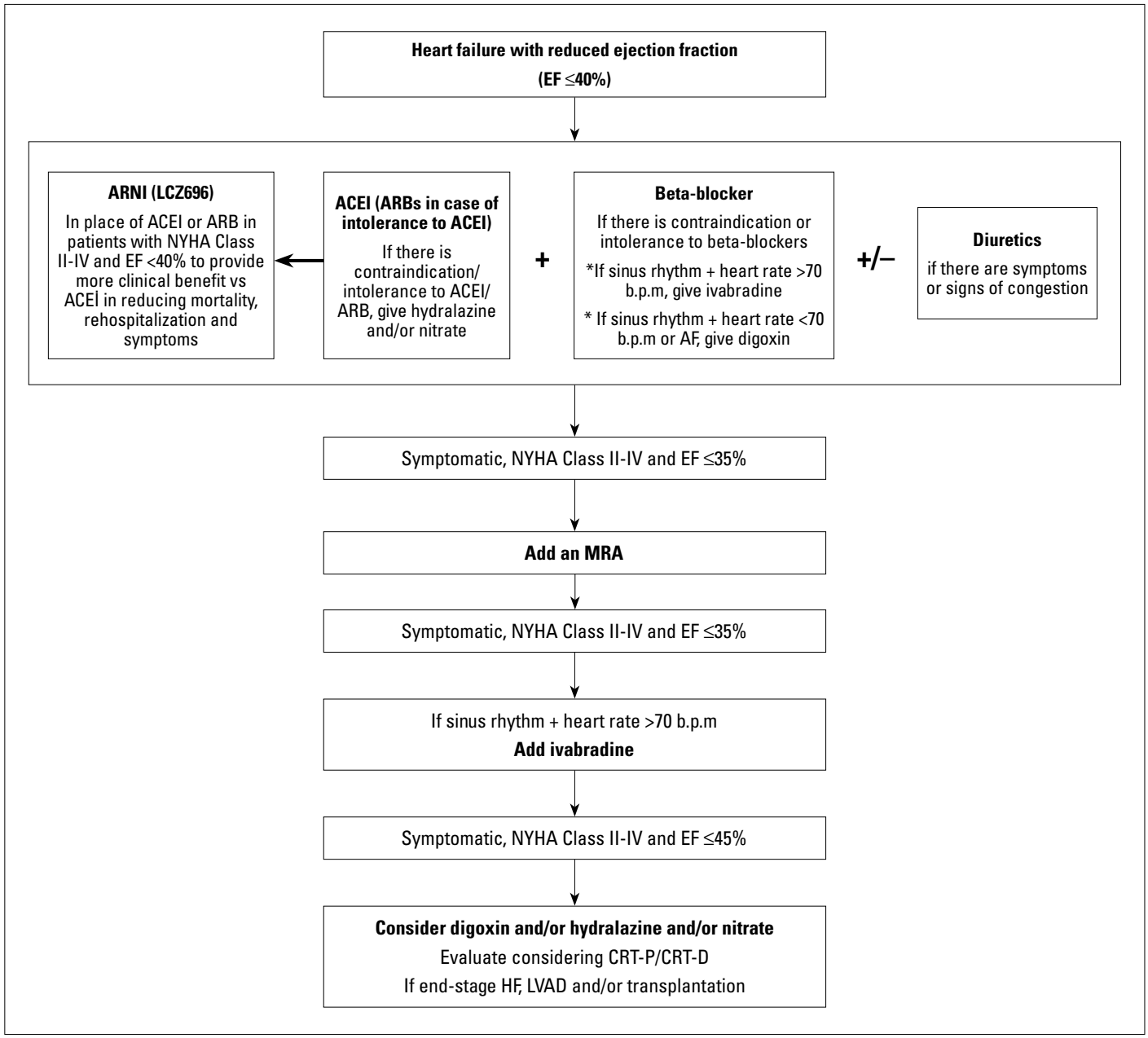


Figure 1. Treatment algorithm in chronic heart failure

ACEI – angiotensin converting enzyme inhibitor; AF – atrial fibrillation; ARBs – angiotensin receptor blocker; ARNIs – angiotensin receptor neprilysin inhibitors; CRT - cardiac resynchronisation therapy; D – defibrillator; EF – ejection fraction; LVAD – left ventricular assist device; MRAs – mineralocorticoid receptor antagonist; NYHA – New York Heart Association; P – pacemaker

en to reduce mortality. ACEIs reduce both mortality and re-hospitalization and have been shown to be effective in all patients who have mild, moderate or severe HF with or without coronary artery disease (CAD). Candesartan, valsartan and losartan among the ARBs were shown to reduce cardiovascular death or hospitalization significantly. However, their efficacy on all-cause mortality alone has not been clear (3, 4).

In the BB group; bisoprolol, carvedilol and extended-release metoprolol succinate have been demonstrated to decrease all-cause mortality, cardiovascular mortality, HF-related mortality or sudden deaths. Their clinical benefits are observed in female and male patients with or without CAD and with or without diabetes mellitus (DM). Nebivolol was shown to reduce all-cause mortality or hospitalization in elderly population (>70 years). However, its effect on mortality alone has not been demonstrated (13).

MRAs are the third drug group which is effective on mortality. In the RALES Trial (14), spironolactone reduced all-cause mortality, sudden cardiac death and hospitalization. Eplerenone was shown to reduce all-cause mortality in patients with both post-MI HF (15) and NYHA Class II-IV HF-REF (16).

Ivabradine provides a reduction in heart rate by exerting its effect through the inhibition of If channels located in the sinus node. In patients who have NYHA Class II-IV HF with EF <35%, resting heart rate >70 b.p.m. and in sinus rhythm, ivabradine treatment added to standard background HF therapy including BB, ACEI, MRA and diuretic was shown to significantly reduce cardiovascular death or HF hospitalization as well as death from HF alone and HF hospitalization alone.

Hydralazine + isosorbide dinitrate combination has been shown to reduce mortality and hospitalization in African-Americans with NYHA Class III-IV HF and EF ≤45%, who were receiving diuretic, digoxin, ACEI (ARB), BB and spironolactone therapy. In order to reduce the risk of death in patients with left ventricular EF ≤45% who cannot tolerate ACEIs/ARBs, hydralazine + nitrate combination is recommended as Class IIa indication by the American College of Cardiology Foundation (ACCF) / American Heart Association (AHA) guidelines and Class IIb indication by the European Society of Cardiology (ESC) guidelines (3, 4). In the ACCF/AHA guidelines, this combination is given as Class I recommendation to reduce mortality in symptomatic African-Americans in functional NYHA Class III-IV despite optimal medical treatment (4). Drugs with proven effect on mortality are shown in Table 4.

In the recent PARADIGM-HF Trial, the ARNI LCZ696 consisting of a new molecule sacubitril (neprilysin inhibitor) and valsartan (ARB) was compared with the enalapril therapy in patients with HF-REF. Patients with left ventricular EF ≤40% in NYHA Class II-IV were included in this trial and randomized to receive LCZ696 200 mg b.i.d. or enalapril 10 mg b.i.d.. Due to the favorable effect of LCZ696 on mortality, the trial was terminated prematurely. When compared to enalapril, ARNI was shown to significantly reduce primary end-points of cardiovascular (CV) mortality or HF hospitalization by 20%, CV mortality alone by 20%, HF hospitalization alone by 21% and all-cause mortality by 16%. The most frequent side effect was hypotension (17).

Table 4. Drug groups in HF-REF and their effects on mortality/morbidity

Drug group	Efficacy in mortality / morbidity (based on major studies)
ACEIs	+ (CONSENSUS, SOLVD, SAVE, AIRE, TRACE)
ARBs	+ (CHARM Alternative, Val-HEFT)
BBs	+ (US Carvedilol, CIBIS II, MERIT HF, COPERNICUS, CAPRICORN)
MRAs	+ (RALES, EMPHASIS HF)
Ivabradine	+ (SHIFT)
LCZ 696	+ (PARADIGM-HF)
Digoxin	± Hospitalization (DIG)
H + ISDN	+ (V-HeFT I, V-HeFT II, A-HeFT)
Diuretics	?

ACEIs – angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers; BBs – beta blockers; H – hydralazine; HF-REF – heart failure with reduced ejection fraction; ISDN – isosorbid dinitrate; MRAs – mineralocorticoid receptor antagonists

No group of drugs has been shown to have significant effect on mortality in patients with HF with preserved ejection fraction (HF-PEF) to date.

4.3 Does beta-blocker therapy have any effect on mortality in atrial fibrillation?

Both ESC and ACCF/AHA guidelines recommend BB therapy as Class I recommendation in HF-REF patients. This group of drugs reduces both mortality and morbidity. There is no specific clinical trial evaluating mortality benefit of beta blocker treatment in patients with AF. However some meta-analyses published in literature examined mortality benefit of BB in this group of patients. In a meta-analysis in 8,500 HF patients, BB therapy was found to have no effect on mortality and much less beneficial effect on re-hospitalization in patients with AF compared to patients in sinus rhythm (18). Also, in a recent meta-analysis including more than 18,000 patients, BB therapy was shown to have no effect on all-cause mortality in HF patients with AF (19). Randomized, prospective trials are needed to elucidate the effect of BBs on mortality in this group of patients. However, in all patients who have HF-REF with or without AF, BB therapy should be used and continued until this matter is clarified with randomized, prospective trials.

4.4 Which drugs are effective on symptoms, quality of life and re-hospitalization?

The favorable effects of ACEIs/ARBs, BBs and MRAs on survival as well as on symptoms, quality of life and hospitalization have been proven in major clinical trials. Hydralazine and nitrate combination has been shown to be very effective particularly in patients who cannot receive ACEIs/ARBs. This beneficial effect is more prominent in African-Americans. However, favorable ef-

fects of adding H-ISDN to the current ACEI/ARB therapy are not clear in other American populations (20, 21).

Diuretics are also very effective agents in the improvement of symptoms and quality of life. All patients with congestion and fluid retention should receive diuretic therapy. Even though digoxin has no effect on mortality, it is known to be an effective agent in symptoms and re-hospitalization. In the DIG Trial, digoxin has been demonstrated to reduce the frequency of hospitalization in symptomatic HF patients in sinus rhythm (22).

Ivabradine in patients with EF <35%, in sinus rhythm and with heart rate >70 b.p.m was not found effective in reducing cardiovascular death alone or all-cause mortality alone, however, it was shown to reduce cardiovascular death or HF hospitalization and also incidence of recurrent hospitalization (23).

4.5 How to select evidence-based drugs in terms of NYHA, EF and heart rate?

According to the ESC and ACCF/AHA guidelines, drug choice should be ACEIs/ARBs and BBs in patients with NYHA Class I-IV with left ventricular dysfunction, MRAs in patients with NYHA Class II-IV, ivabradine in patients with NYHA Class II-IV who are in sinus rhythm, with a heart rate >70 b.p.m. and symptomatic despite optimal therapy, hydralazine+nitrate combination in African-Americans with NYHA Class III-IV who are symptomatic despite optimal treatment, diuretics in patients with NYHA Class II-IV who have volume overload, and digoxin in patients with NYHA Class II-IV who are still symptomatic despite optimal treatment (3, 4) (Table 5). Drug selection according to the ejection fraction is similar in both guidelines. ACEI/ARB and BB therapy should be initiated in every patient with left ventricular EF ≤40%. MRAs can be scheduled to be used in patients with EF ≤35%. In patients in sinus rhythm with elevated heart rate and EF ≤35% despite the BB therapy, the ESC guidelines state that ivabradine therapy can be added whereas American guidelines have no recommendation about this drug. In patients with EF ≤45% who are symptomatic despite optimal treatment, adding digoxin or hydralazine+nitrate combination can be considered (3, 4).

ACEIs/ARBs have no effect on heart rate. BB use and dose adjustment according to heart rate are important. If the heart rate is <60 b.p.m., initiating BB therapy should be avoided. When the heart rate becomes <50 b.p.m. during BB use, the drug should be discontinued or the dose reduced to half. Adding ivabradine should be considered in patients with a heart rate >70 b.p.m. despite optimal BB dose to decrease the heart rate below 70 b.p.m. (3). In patients with AF, BBs and, if necessary, digoxin should be given to control heart rate (3, 4).

In patients with systolic blood pressure below 80 mm Hg, ACEIs/ARBs, BBs and hydralazine-nitrate combination should not be given. Ivabradine has no effect on blood pressure. MRAs rarely cause a reduction in blood pressure when used in antifibrotic doses used in HF. When adjusting the doses of these drugs according to the blood pressure, not only the blood pressure levels but also the symptoms of hypotension should be considered.

4.6 Is it possible to discontinue drug therapy if EF improves along with symptoms?

In HF patients in which EF improves along with symptoms, there is not enough evidence regarding the management of drug therapy. There is limited data concerning drug discontinuation after the improvement of ventricular functions in patients with acute myocarditis and peripartum cardiomyopathy. Discontinuation of ACEI and BB therapy in chronic HF patients was reported to have unfavorable effects on cardiac functions, symptoms and end-points (24). In selected patients in whom symptoms and EF completely improved, discontinuation of BB and ACEI therapy step by step can be reasonable approach by decreasing the doses gradually and monitoring cardiac functions closely.

4.7 Are dose titration intervals and duration the same for every drug and patient?

Generally guidelines recommend that ACEI, ARB, BB and MRA dose titrations should be performed as doubling the doses every 2-4 weeks and initiating with 1/8 of the dose (3, 4). How-

Table 5. Drug therapy according to New York Heart Association functional classification

	Heart failure with reduced ejection fraction			
	NYHA I	**NYHA II**	**NYHA III**	**NYHA IV**
ACEI	+	+	+	+
ARBs	+	+	+	+
BBs	+	+	+	+
MRAs	–	+	+	+
Ivabradine	–	+	+	+
Digoxin	–	+	+	+
Diuretics	–	–	+	+
Hydralazine+nitrate	–	–	+	+

ACEI – angiotensin converting enzyme inhibitor; ARBs – angiotensin receptor blocker; BBs – beta-blockers; MRAs – mineralocorticoid receptor antagonists; NYHA – New York Heart Association

ever, this general recommendation should not be considered as an absolute rule to be adhered to for every patient and every drug. In clinical trials, generally, the duration of reaching the target dose or tolerated dose had taken 4 weeks on average with ACEIs/ARBs, approximately 6 weeks with BBs and 4-6 weeks with MRAs for stable patients. A slower up-titration with BBs and slightly faster up-titration with ACEIs/ARBs depending on blood pressure and renal functions can be considered. A slightly faster up-titration of MRA can be performed according to the creatinine and potassium levels tested every 3-7 days. It may be appropriate to initiate in a level of $^1/_4$ of the target dose of drugs in patients with normal or mildly elevated blood pressure, normal renal functions and normal potassium levels. A faster up-titration can be considered in NYHA Class I-II patients who are clinically stable and asymptomatic. In case of adverse effects, switching to one or two previous doses and subsequent up-titration in a longer period of time can be considered.

Initial dose of digoxin should be decided according to age, weight and renal functions. Loading dose of digoxin is not recommended. Ideal dose adjustment should be performed with plasma digoxin level measurements, if possible. Hydralazine and/or nitrate combination is initiated at a very low dose and up-titration is performed according to the blood pressure response. In clinical trials, the decision for up-titration of the hydralazine and/or nitrate dose has been left to the discretion of the physician and when the side effects resolved and blood pressure was controlled, the dose was up-titrated (25).

It is recommended to initiate ivabradine as 5 mg b.i.d. and, according to the protocol of its clinical trial, to increase to 7.5 mg b.i.d. depending on the heart rate and side effects of the drug after 15 days (26).

4.8 Is it necessary to achieve the target dose for mortality benefit?

The basic rule in treatment is to start ACEI/ARB, BB and MRA therapies with the lowest dose and to increase to the target dose the benefit of which was shown in the clinical trials. The second basic rule is to increment the dose to the maximum tolerated dose in patients who cannot tolerate the target dose. Another important rule is to use these drugs even if in low doses rather than not using them at all. There are subgroup analyses supporting that mortality benefit is observed even 6.25 mg daily dose of carvedilol and 1.25-3.75 mg daily dose of bisoprolol. After initiating ACEI/ARB therapy, adding BB therapy before achieving the target dose is important in terms of mortality and morbidity (27). In a clinical trial conducted in Austria, it was demonstrated that adjusting treatment in accordance with the guidelines reduced all-cause mortality in patients with HF-REF (27). When the study group is examined, the percentage of patients who received ACEI/ARB, BB and MRA therapies were 90.5%, 87.8% and 42.7%, respectively and the percentage of patients receiving drugs in target doses was less than 50%. The majority of patients who could not achieve target doses with an adjustment of the treatment in accordance with the guidelines at the end of follow-up could receive more than 50% of the target doses. Even under these circumstances, the favorable effects of therapy were demonstrated. In patients with recurrent hospitalization, ischemic cardiomyopathy, renal disorder and advanced age, it was less possible to achieve the target doses. Target doses were more easily achieved in patients with elevated natriuretic peptide levels and hypertensive patients. In another trial conducted in Spain, target doses were achieved with ACEI, ARB, BB and MRA therapies in 16.2%, 23.3%, 13.2% and 23.5% of the HF patients, respectively (28). Even though target doses were not achieved after CRT, use of higher doses of neurohumoral blockers had favorable effects on survival (29). Use of basic drugs even in low doses is expected to have favorable effects despite having less effect on mortality and morbidity (4).

5.0 Angiotensin converting enzyme inhibitors/ Angiotensin receptor blockers – Mehmet Eren

5.1 Which ACEIs/ARBs should be chosen?

Although angiotensin converting enzyme inhibitors are accepted to have a class efficacy in HF, all ACEIs individually do not have enough evidence in terms of their effectiveness and safe doses supported by randomized-controlled trials. Therefore, it is recommended that ACEIs proven to be effective in HF trials should be used in HF therapy (Table 6).

It has been demonstrated that morbidity significantly reduced with the use of both candesartan (36, 37) and valsartan (38) when angiotensin receptor blockers (ARBs) were added to the treatment of HF patients with symptomatic reduced left ventricular ejection fraction (LVEF) who are intolerant to ACEIs.

Table 6. ACEIs and their doses with proven efficacy in patients with HF in randomized, controlled trials

ACEIs	Patient characteristics	Trial	Starting dose (mg)	Target dose (mg)
Captopril	AMI	SAVE (30)	3x6.25	3x50
Enalapril	CHF	CONSENSUS (31), SOLVD (32)	2x2.5	2x10-20
Lisinopril	CHF	ATLAS (33)	1x2.5-5	1x30-35
Ramipril	AMI	AIRE (34)	1x2.5	2x5/1x10
Trandolapril	AMI	TRACE (35)	1x1	1x4

ACEIs – angiotensin converting enzyme inhibitors; AMI – acute myocardial infarction; CHF – chronic heart failure

Although candesartan has been shown to reduce mortality in major trials (36, 37) the mortality effect of valsartan was demonstrated in a small subgroup of Val-HeFT Trial (38) (Table 7). In the ELITE-II Trial, the only trial in which ARBs were directly compared to ACEIs in HF, losartan was not found as effective as captopril on mortality and morbidity (39). In this trial, losartan was suggested to be less effective than captopril because of its low dose. Indeed, in the HEAAL Trial, (40) 150 mg losartan was found to be more effective compared to 50 mg losartan in terms of primary end-point (41). However, there is no comparative trial of losartan versus ACEIs or placebo. Therefore, current guidelines recommend the use of losartan with a careful consideration.

5.2 Does the history of myocardial infarction affect the selection of ACEIs/ARBs?

It is not known whether ACEIs initiated in the first week after AMI have class efficacy regarding their clinical benefit. Thus, ACEIs proven to be beneficial in clinical trials should be used in these patients following myocardial infarction (Table 8).

In the OPTIMAAL (42) which is one of the two trials conducted with ARB in patients in whom HF developed after myocardial infarction, the mortality effect of losartan was lower than captopril whereas in the VALIANT (41), valsartan was found to be as effective as captopril. When the valsartan arm in the VALIANT Trial was compared to the placebo arm of other trials, the results were found to be similar to those of ACEIs. Valsartan is therefore a good alternative to ACEIs after myocardial infarction (41, 43).

5.3 What are the alternative therapies if ACE inhibitor/ ARB is contraindicated?

The contraindications of ACEI and ARB are given in Table 9. The side effects of ACEIs are related to either suppression of angiotensin or quinine elevation (Table 10). In the cases of quinine elevation, ARBs can be a good alternative to ACEIs (36, 38). In the cases of angiotensin suppression and pregnancy (44), ARBs cannot be prescribed either. In this case a hydralazine-nitrate combination can be used (25, 44-46). In non-severe aortic stenosis, ACEIs, ARBs and a hydralazine-nitrate combination can be used (47). H-ISDN combination is initiated with 37.5/20 mg tid and 70/40 mg tid target dose is achieved. None of these agents are given in the presence of severe aortic stenosis because severe hypotension and syncope may develop. In severe aortic stenosis with asymptomatic left ventricular dysfunction or symptomatic HF, percutaneous or surgical valve replacement or balloon valvuloplasty is performed and then ACEIs/ARBs can be used. Otherwise, vasodilator should not be used in severe aortic stenosis.

Table 7. ARBs and their doses with proven efficacy in patients with HF in randomized, controlled trials

ARBs	Patient characteristics	Trial	Starting dose (mg)	Target dose (mg)
Candesartan	CHF	CHARM (36,37)	1x4-8	1x32
Valsartan	CHF	Val-HeFT (38)	2x40	2x160
Valsartan	AMI	VALIANT (41)	2x20	2x160

AMI – acute myocardial infarction; ARBs – angiotensin receptor blockers; CHF – chronic heart failure

Table 8. Randomized ACEI or ARB trials conducted in symptomatic or asymptomatic patients with reduced ejection fraction after myocardial infarction

Class	Trial	Comparison	Effect on primary results
ACEI	SAVE (30)	Captopril-Placebo	19% reduction
ACEI	TRACE (35)	Trandolapril-Placebo	22% reduction
ACEI	AIRE (34)	Ramipril-Placebo	27% reduction
ARB	OPTIMAAL (42)	Losartan-Captopril	Captopril is better
ARB	VALIANT (41)	Valsartan-Captopril	Captopril and valsartan are similar

ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker

Table 9. Contraindications for ACEI and ARB use

Contraindications for ACEI	Contraindications for ARBs
Bilateral renal artery stenosis	Bilateral renal artery stenosis
Pregnancy	Pregnancy
Serum creatinine >2.5 mg/dL	Serum creatinine >2.5 mg/dL
Serum potassium >5 mEq/L	Serum potassium >5 mEq/L
Severe aortic stenosis	Severe aortic stenosis
History of angioedema	

ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker

Table 10. Main side effects of ACEIs

Side effects related to angiotensin suppression	Side effects related to quinine elevation
1. Hypotension	1. Cough
2. Worsening of renal functions	2. Angioedema
3. Hyperkalemia	

6.0 Beta-blockers – Mehmet Eren

6.1 Which one of the 4 beta-blockers recommended in the treatment is better?

Four BBs (metoprolol succinate, bisoprolol, carvedilol and nebivolol) are recommended based on data from major trials conducted for the treatment of HF. Since there are no randomized trials comparing the BBs used in HF, no superiority can be suggested. However, based on the results (Table 11) obtained from the trials and on the pharmacological properties of beta-blockers (Table 12), in certain conditions, some beta-blockers may be preferred to others.

Cardioselectivity: Cardioselectivity shows that the drug blocks beta-1 receptors primarily. It should be kept in mind that all BBs also block beta-2 receptors in high doses. Bisoprolol, metoprolol, and nebivolol are less effective on beta-2 receptors. Bisoprolol has the highest cardioselectivity. Cardioselective BBs are preferred over non-selective ones in chronic bronchitis, DM and peripheral arterial disease. It should not be given to patients with bronchospasm, however, if it is mandatory, they should be used in low doses and very cautiously.

Lipid solubility: Hydrophilic BBs without lipid solubility (e.g. atenolol, nadolol and sotalol) cause less side-effects related to the central nervous system, such as nightmares, depression, fatigue and impotence since their passage across the blood-brain barrier is low. However, agents like carvedilol and metoprolol with high lipid solubility are considered more effective in preventing cardiac deaths with better blockade of sympathetic discharge formed in the hypothalamus (48). Lipophilic BBs are metabolized via the liver whereas hydrophilic BBs are renally excreted. The beta-blocker with the highest lipophilicity is carvedilol.

Hepatic metabolism: Since lipophilic BBs undergo first-pass metabolism in the liver, different blood concentrations may occur among patients who receive the same dose and degradation of the drug reduces with the use of drugs which reduce the hepatic blood flow (such as cimetidine) or with liver diseases (such

Table 11. Favorable clinical outcomes obtained from clinical trials on beta-blockers use in HF

Effect	Trials	Beta-blocker
Reduction in total mortality	MERIT-HF (51, 52), CIBIS-II (53), COPERNICUS (54)	Metoprolol CR/XL, bisoprolol, carvedilol
Reduction in cardiovascular mortality	MERIT-HF, CIBIS-II, COPERNICUS,	Metoprolol CR/XL, bisoprolol, carvedilol
Reduction in cardiovascular mortality or HF hospitalization	MDC (55), CIBIS-II, MERIT-HF, COPERNICUS, US Carvedilol (56), SENIORS (57)	Metoprolol tartrate, Metoprolol CR/XL, bisoprolol, carvedilol, nebivolol
Reduction in HF symptoms	CIBIS-II, MERIT-HF, US Carvedilol	Metoprolol CR/XL, bisoprolol, carvedilol

Table 12. Pharmacological properties of beta-blockers used in heart failure and their doses

Properties	Metoprolol	Bisoprolol	Carvedilol	Nebivolol
B1-blockade	++++	++++	++++	++++
B2-blockade	++	++	+++	+
A1-blockade	0	0	++++	0
ISA	0	0	0	0
Lipid solubility	++	++	+++	+++
Hepatic elimination	++++	++	++++	++
Half-life	2-6 hours	9-12 hours	6 hours	10 hours[a]
Peripheral vasodilation	0	0	+	+ (with NO)
Anti-oxidant	0	0	+	0
Starting dose (mg)	1x12.5-25	1x1.25	2x3.125	1x1.25
Target dose (mg)	1x200	1x10	2x25-50	1x10

[a]Half-life of nebivolol metabolites is 24 hours
ISA – intrensic sympatomimetic activity; NO – nitric oxide

as cirrhosis). In these cases, dose adjustment of carvedilol and metoprolol in particular may be necessary.

Effect on oxidative stress: Another toxic effect of increase in catecholamine is the formation of free radicals and damage due to oxidative stress (49). In HF, free radicals in circulation contribute to the progression of the disease and probably cause apoptosis. Carvedilol is known to have antioxidant properties (50). Beta-blockers except carvedilol should therefore be preferred in severe Chronic Obstructive Pulmonary Disease. Since carvedilol provided a better improvement in clinical results than metoprolol tartrate in the COMET Trial, carvedilol should be used instead of metoprolol tartrate (58). As the SENIORS Trial examined the efficacy of nebivolol in elderly patients, nebivolol is a BB which can be preferred in the population >70 years (57). The CIBIS-III Trial examined which one of the BB (bisoprolol) and ACEI (enalapril) treatments should be initiated first in the form of a single drug therapy, and then used as a combination. No difference was determined in the results (59). If ACEIs are to be added later, bisoprolol is the BB of choice. In one meta-analysis, in patients with HF of ischemic origin, metoprolol succinate was found to be superior to carvedilol; whereas in HF of non-ischemic origin, carvedilol was found to be superior (60).

6.2 How can we determine whether fatigue and exercise intolerance are caused by beta-blockers or HF?

In a meta-analysis examining the side effects of BB use in patients with HF, myocardial infarction or hypertension; fatigue and exercise intolerance related to BBs were observed in 1.8% of patients and 1 in 57 patients treated with BBs for one year (61). These side effects were observed less with last generation BBs (61). The mechanism of fatigue and exercise intolerance associated with BB therapy is not fully known. In patients with HF receiving BB therapy, development of fatigue or exercise intolerance may originate from the disease itself or the effect of BB therapy. In this case, the BB dose should be reduced to half. If symptoms improve, the reason is BB and the treatment is continued with the dose the patient can tolerate. If the symptoms do not improve, they are related to the disease and the HF treatment should be optimized.

6.3 How should beta-blocker therapy be managed in case of impotence?

Normal sexual function occurs as a result of the interaction of psychological, hormonal, vascular and neurological factors. On the other hand, erection is a vascular phenomenon and nitric oxide (NO) plays an important role in this phenomenon (62). Impairment of vascular smooth muscle relaxation developing as a result of the NO-cGMP pathway being affected is the final common pathway leading to erectile dysfunction (63).

It was reported that libido and erectile function are affected in three fourths of patients with HF (64). The causes and mechanisms that may lead to erectile dysfunction in HF patient are summarized in Table 13 (65). Erectile dysfunction in patients treated with BBs is only 0.5%, not as high as it was believed before (61). Although the mechanism of erectile dysfunction with BBs is not

Table 13. Causes of erectile dysfunction in patients with HF

Causes of HD	Mechanisms
Psychological	
Depression	Reduced libido
Performance anxiety	Increased sympathetic tonus
Anti-psychotic drugs	Selective serotonin reuptake inhibitors
Fear	
Atherosclerosis	Reduced penile artery flow
	Endothelial dysfunction
Cardiovascular exercise intolerance	Heart rate incompetence
	Reduced stroke volume
Impaired vessel tonus response	Impaired endothelial independent vasodilation
	Endothelial dysfunction
	Elevated endothelin-1
	Elevated noradrenaline
	Reduced prostacycline
HF drugs	
Beta-blockers (some)	Not known
Digoxin	Corporal smooth muscle sodium pump inhibition
Spironolactone	Androgen suppression
Diuretics	Not known

fully known, potentializing corporal smooth muscle contraction via alpha-1 receptor may lead to this condition. Carvedilol and nebivolol have some advantages in this regard.

The first step in the treatment of HF patients with erectile dysfunction is to optimize HF treatment. If possible, drugs causing sexual dysfunction should either be discontinued or switched. Digoxin and thiazide diuretics should be discontinued and carvedilol or nebivolol should be preferred among BBs. As an aldosterone antagonist, eplerenone, which is more selective with less androgenic effect, is preferred over spironolactone. If complaints continue after these measures, phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, vardenafil and tadalafil), which is the main treatment for erectile dysfunction, should be administered. Before initiating these drugs, the patients should be classified as mild-, moderate- and high-risk regarding the risks that they may experience during sexual intercourse. Most low-risk patients have NYHA Class I functional capacity, and PDE-5 inhibitors can be safely given. Whereas high-risk patients are NYHA Class III-IV or decompensated patients, and sexual intercourse is forbidden in this group. After the patients are stabilized, they are reevaluated in terms of erectile dysfunction treatment. Moderate-risk patients (in NYHA Class II or with asymptomatic left ventricular systolic dysfunction) should be evaluated with additional stress tests.

It was demonstrated that sildenafil has been well tolerated and improved erectile dysfunction in 25-100 mg doses in patients with mild to moderate HF (66). Although such safety or efficacy has not been shown with vardenafil and tadalafil, vardenafil can be used in solving the problem. However, tadalafil should not be used in these patients due to its long half-life.

As a result, sildenafil should be initiated in 25-50 mg doses and incremented to 100 mg for the treatment of erectile dysfunction in patients with HF. These drugs are contraindicated in combination with nitrate or NO donors (nitroprusside, molsidomine) as they increase the hypotensive effects of nitrates.

6.4 What are the alternative therapies in the presence of beta-blocker contraindication?

Beta-blocker contraindications and adverse events during their use are shown in Table 14.

In patients with HF who have contraindication or intolerance for BBs, ivabradine or digoxin can be given as an alternative. If the patient has AF, only digoxin can be used to slow ventricular rate. If the patient is in sinus rhythm, primarily ivabradine and as a second alternative digoxin can be given (Table 15) (3).

7.0 Mineralocorticoid receptor antagonists – Mehmet Eren

7.1 What are the antifibrotic and diuretic doses of MRAs?

Mineralocorticoid receptor antagonists have both antifibrotic and diuretic effects. Spironolactone is used more as a diuretic. The doses of 25-50 mg spironolactone used in the RALES Trial have a more antifibrotic effect and their diuretic effect is minimum at these doses (67). The diuretic effect of spironolactone is observed in doses above 100 mg a day (68).

In HF, there is a reduction in cardiac output, and this leads to the activation of renin angiotensin aldosterone system (RAAS), sympathetic nervous system and arginine vasopressin and eventually volume and salt retention in the body. Therefore, there is a hyperaldosteronism in HF.

Hyperaldosteronism is also present in hepatic cirrhosis. In the treatment of ascites in patients with cirrhosis, a primarily high dose of spironolactone (200 mg bid) is used; whereas in HF, loop diuretics are used primarily for pre-existing congestion. However, loop diuretics cause more elevation in hyperaldosteronism. Hyperaldosteronism is known as a risk factor for myocardial and vascular fibrosis. Similar to cirrhosis, high doses of spironolactone are expected to be beneficial in HF. In a HF trial including a low number of patients, spironolactone treatment at doses of 200 mg b.i.d. caused a significant increase in sodium elimination with a nonsignificant increase in potassium levels. However, more trials are needed on the antifibrotic and clinical effects of diuretic doses of spironolactone in HF.

Table 14. Beta-blocker contraindications and adverse events during their use

Contraindications	Adverse events with use
Asthma	Hypotension
Sinus bradycardia (<50 b.p.m)	Bradycardia
Sick sinus syndrome	Fluid accumulation
Second or third degree AV block	Worsening of HF
Bronchospasm	
Severe claudication	
Decompensated HF- in acute phase	

Table 15. Drugs recommended as the alternative therapy of beta-blockers in HF according to the ESC 2012 HF guidelines (3)

Drug	Indication	Recommendation and evidence level
Ivabradine	Can be considered to reduce hospitalization in patients with BB intolerance, receiving ACEIs (ARBs) and MRAs (ARBs), who are in sinus rhythm, with LVEF ≤35%, HR ≥70 b.p.m.	IIb-C
Digoxin	In order to reduce hospitalizations in patients receiving ACEIs (ARBs)+ MRAs (ARBs), who are in sinus rhythm, with LVEF ≤45%	IIb-B

7.2 What are the cautions in the dose management of MRAs?

The most important risk of MRA treatment in patients with HF is the development of hyperkalemia (14, 16). The risk of severe hyperkalemia in patients with HF receiving MRA is approximately 2-3% (14, 16). This risk is higher in patients with renal failure. Because of the risk of hyperkalemia, both the patient selection and the treatment follow-up should be performed carefully. In this case, renal functions and serum potassium levels of patients are helpful markers in guiding MRA therapy. What to do to reduce the risk of severe hyperkalemia is summarized in Table 16.

7.3 Can MRA be used every other day?

According to the RALES Trial protocol, if potassium had increased while receiving 25 mg spironolactone, 25 mg every other day protocol was used instead of half the dose (14). In the EMPHASIS-HF Trial, in patients with an estimated glomerular filtration rate (eGFR) value of 30-49 mL/min/1.73 m^2, eplerenone was initiated at 25 mg every other day instead of daily use and subsequently the dose was up-titrated to 25 mg daily after 4 weeks (69). In the same trial, in patients receiving 25 mg daily doses of eplerenone, when renal dysfunction and potassium elevations were observed, the dose was adjusted to 25 mg every other day.

Based on the results of these two trials, in clinical practice, low doses of MRA can be used every other day in patients with HF who have developed (serum K+=5.5-5.9 mmol/L) or at risk of developing hyperkalemia (particularly, in elderly patients or in patients with eGFR=30-49 mL/min/1.73 m^2).

7.4 What are the alternative therapies in the presence of MRA contraindication?

In Table 17, contraindications and conditions requiring caution are given. Since eplerenone is a specific MRA, it is preferred for the anti-androgenic side effects of spironolactone (e.g. gynecomastia). In cases where both of MRAs are not used, there is no agent to be given for mineralocorticoid blockage. In HF treatment, if the patient is still symptomatic despite ACEI+BB therapy, in patients who have contraindication or intolerance to MRA, ARBs can be added (37, 70). In patients receiving ACEI, adding ARB to the ACEI therapy has been primarily shown to pro-

Table 16. Recommendations related to the use of MRAs in patients with HF (3)

Condition	What to do
Serum K^+ >5 mEq/L Serum creatinine >2.5 mg/dL (221 mmol/L) eGFR <30 mL/min/1.73 m^2	MRAs use is contraindicated
In ACEI+ARB users Concurrent with potassium-sparing diuretics Concurrent with potassium supplement	MRAs use is contraindicated
Should be initiated in a low dose and up-titrated to the target dose in 4-8 weeks	Initial dose; Spironolactone 25 mg daily Eplerenone 25 mg daily 25 mg every other day in elderly patients or in patients with eGFR=30-49 mL/min/1.73 m^2
	Target dose; Spironolactone 25-50 mg daily Eplerenone 50 mg daily
Follow-up intervals after initiating the drug	At 1, 4, 8 and 12 weeks At 6, 9 and 12 months Subsequently every 4 months
Markers to be measured during follow-up	Serum K^+, Na^{+2} and creatinine eGFR
During follow-up; Serum K^+ = 5.5-5.9 mEq/L Serum creatinine = 2.5-3.5 mg/dL (221-310 mmol/L) eGFR <30 mL/min/1.73 m^2	Reduce the dose to 25 mg if 50 mg is used Reduce the dose to 25 mg every other day if 25 mg is used Discontinue if 25 mg is used every other day
During follow-up; Serum K^+ >6 mEq/L Serum creatinine >3.5 mg/dL (310 mmol/L) eGFR <20 mL/min/1.73 m^2	Drug should be discontinued and potassium lowering therapy should be initiated

ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; eGFR – estimated glomerular filtration rate; K – potassium; Na – sodium

Table 17. Contraindications and cautions in MRA use

Contraindications	Conditions requiring caution
Hyperkalemia (initial Serum K^+ >5 mEq/L)	Porphyria (only for spironolactone)
Anuria	Pregnancy and lactation
Acute or severe renal failure (serum creatinine >2.5 mg/dL-221 mmol/L or eGFR <30 mL/min/1.73 m^2)	Child Pugh A or B hepatic failure (electrolytes should be closely monitored)
Addison's Disease	Moderate to severe renal failure (serum creatinine >1.8 mg/dL-150 mmol/L or eGFR=30-49 mL/min/1.73 m^2)
Hyponatremia (Na^+ <135 mmol/L)	Diabetic microalbuminuria
Hypersensitivity to MRAs	
Concurrent use with potassium-sparing diuretics	Elderly patients (potassium levels should closely be monitored)
Concurrent use with potassium supplement	Some drugs and food intake
Concurrent use with ACEI+ARB combination	
Concurrent use of eplerenone with strong cytochrome P450 3A4 inhibitors (ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir)	
Severe hepatic failure (Childs Pugh-C)	

ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; eGFR – estimated glomerular filtration rate; K – potassium; Na – sodium

vide morbidity benefit but also the combined endpoints of mortality and morbidity have been improved. In the Val-Heft Trial, valsartan, which was added to the treatment of patients receiving ACEIs, improved morbidity with no effect on mortality (70). In the CHARM-Added Trial, both mortality and morbidity reduced with the addition of candesartan to the treatment of patients receiving ACEIs (37). In these trials, adding ARB to the ACEI therapy caused more side effects (dizziness, hypotension, renal dysfunction and hypercalcemia). So, patients should be closely monitored if ARB will be added to their ACEI therapy.

There are controversial findings regarding ACEI+BB+ARB triple combination. In the Val-HeFT Trial, valsartan included in this combination has been found to increase mortality and morbidity (70) whereas this negative outcomes were not confirmed in the VALIANT Trial in post-MI patients (41). This triple combination with candesartan in the CHARM-Added Trial provided a reduction in the combined endpoints of mortality and morbidity (37).

8.0 Diuretic treatment – Dilek Yeşilbursa

8.1 Which diuretic should be administered to which patient and how?

Unlike BBs, ACEIs and MRAs, the effects of diuretics on mortality and morbidity were not investigated. However, their use in relieving shortness of breath and edema is recommended regardless of ejection fraction in HF patients with signs and symptoms of congestion (Class I, Evidence B) (3). After evaluating the renal functions and serum electrolytes, the diuretic treatment is initiated in a low dose and the dose is incremented until the clinical signs and symptoms regress. In patients with mild congestion, 2 or 3 times weekly use of thiazide diuretics may be enough in the maintenance of normal intravascular volume. Furthermore, thiazides can be preferred in hypertensive HF patients with mild fluid retention due to their antihypertensive effects. However, daily use of a loop diuretic such as furosemide is necessary in patients with severe congestion or reduced renal function that decreases the effect of thiazides (if GFR is <30-40 mL/min., thiazides are ineffective). Loop diuretics are more potent natriuretics than the other diuretics, particularly in patients with reduced GFR.

In patients without significant signs of congestion, a single daily dose of a loop diuretic is generally enough. 2-3 doses may be required in patients with more severe congestion. In patients whose congestive symptoms persist despite loop diuretics and salt restriction, thiazides or diuretics with similar effects but showing their activity in different localizations on renal tubule (sequential nephron blockade) may be effective. In patients receiving this treatment strategy, serum potassium levels should be monitored carefully and, if necessary, potassium replacement should be performed. Use of thiazide diuretics is limited in the elderly, because glomerular filtration rate (GFR) reduces with age. Loop diuretics are preferred over thiazides in elderly patients.

The guidelines recommend intravenous (IV) treatment in patients with decompensated HF requiring hospitalization (3). IV administration shows a more rapid effect than oral administration. Furthermore, the problem of absorption in oral administration due to intestinal edema is not observed with IV administration. Practically, it is recommended that the IV dose should be twice more than the dose the patient usually receives. However, the ideal dose of treatment and route of administration (bolus or continuous infusion) is not clear. In a trial conducted in patients

hospitalized for reduced ejection fraction and acute decompensation, low dose and high dose administration of furosemide as IV bolus or continuous infusion were compared (71). No difference was observed between the administration of furosemide as intermittent IV bolus and IV continuous infusion. It was observed that a high dose was more effective in symptom relief and regression of congestion signs. Before the patients are discharged, symptoms and signs of congestion should disappear completely and the patients should have been receiving stable oral diuretic therapy for at least 48 hours.

8.2 Can patients self-manage their diuretic dose? How?

Self-adjusting of diuretic dose by patients can be a suitable approach since the requirement of diuretics varies depending on the diet, activity level, NYHA Class and HF Stage.

The aim of diuretic use is to achieve and maintain euvolemia (patient's dry weight) with the lowest dose possible (3). This is possible by adjusting the diuretic dose according to needs. In particular, after achieving dry body weight, dehydration should be avoided as it may cause hypotension or worsening kidney functions (3). Dehydration can reduce cardiac output in patients with HF-PEF and, in HF-REF patients, it may unnecessarily prevent to reach the target dose of other drugs such as ACEIs (or ARBs) and MRAs that may change the course of the disease. Most patients can be educated regarding self-adjusting their diuretic doses by monitoring their congestive symptoms and signs as well as daily body weights. They should be informed that they can increase their diuretic dose if they experience shortness of breath and increase in edema or in >2 kg. weight gain in 3 days and decrease the dose again once the symptoms regress.

8.3 Should diuretic therapy be continued in patients in whom congestion improves?

In HF patients without signs and symptoms of congestion, diuretics have no place in treatment. In this case, their use may be harmful by increasing neurohumoral activation. Diuretics must be used in patients with symptoms and signs of congestion (4). Diuretic therapy should not be discontinued until the signs of congestion resolve. After the patient becomes euvolemic, diuretic therapy may be completely discontinued and the clinical course can be monitored by considering the severity of HF. If congestion does not develop again in clinical follow-up, the patient can be monitored only by basic therapy (ACEI, BB, MRA). However, if congestion signs and symptoms recur in clinical follow-up, continuous diuretic therapy should be continued in doses that can prevent the redevelopment of fluid retention after the patient is brought to euvolemic state again. In patients in whom diuretic therapy is discontinued despite recurrent congestion, frequent hospitalizations related to acute HF manifestation are observed.

8.4 Combinations in diuretic therapy: Which combination for which patient?

Diuretics which are used in the treatment of HF are divided into three main groups according to their mechanisms of action: 1) Loop diuretics: They act by inhibiting Na-K-2Cl channel at the ascending limb of the loop of Henle. 2) Thiazides: They act by inhibiting NaCl reabsorption in the distal tubule. Their strength of effect is less compared to loop diuretics. 3) Potassium-sparing diuretics: They have a weak diuretic effect, in which amiloride and triamterene inhibit Na absorption in distal tubule and collecting ducts, and aldosterone antagonists act by binding to aldosterone receptors. They have a particular place in HF because of reducing mortality. This effect is related to their favorable roles in neurohormonal activation, the diuresis they promote is quite low compared to other diuretics.

Each type of diuretics acts on different parts of the nephron. In combination therapy, furosemide+thiazide, furosemide+spironolactone, thiazide+spironolactone and furosemide+metolazone combinations are considered as useful.

Metolazone is not available in our country. Single preparations of other thiazides except indapamide are also not available. Thiazides are available as combination preparations.

A combination of different diuretic drugs is a method used in overcoming diuretic resistance in patients with refractory edema (4). The combination of thiazide or potassium-sparing diuretics with loop diuretics exerts effect through sequential nephron blockade in diuretic resistance. While diuretic effect increases with the combination of loop diuretics and thiazides, since the combination also increases the risk of hypokalemia, hyponatremia and renal dysfunction, close monitoring of the patient is required (3).

Loop diuretics and thiazides cause severe reductions in potassium levels and may consequently cause lethal arrhythmias. In order to prevent this, potassium-sparing diuretics can be used as an add-on therapy to the other diuretics. Generally, these agents have a weak diuretic effect. They are usually insufficient in controlling congestion symptoms when used alone. If the symptoms cannot be controlled despite ACEI and diuretic therapy or hypokalemia persists despite ACEI therapy, potassium-sparing diuretics are recommended to be added to the treatment. Aldosterone antagonists should be preferred over other potassium-sparing diuretics.

8.5 Do low dose combinations have an advantage over high dose single use?

Diuretics should be used in the lowest dose that can improve fluid and sodium retention. This dose is generally determined for each patient by slowly incrementing the dose. Loop diuretics are the most preferred agents because of their fast and potent effects. High-dose diuretic use may lead to excess diuresis. In this case, hypotension and renal dysfunction related to a reduction in intravascular volume may develop. Diuretics are known to cause activation of both renin-angiotensin-aldosterone sys-

tem and sympathetic nervous system. These agents may reduce cardiac output by causing loss of fluid and sodium and they may cause an increase in renin and aldosterone levels in peripheral circulation.

Thiazides and spironolactone are frequently used in combination with loop diuretics. If needed, a combination in low doses is more effective compared to high-dose single use and causes less side effects.

Although thiazides have insufficient diuretic effect when used alone in HF, if administered in combination with loop diuretics, a significant increase in urine output may be provided with significant reduction in complaints. Thus, post-diuretic sodium retention which is observed with loop diuretic therapy is prevented due to the long half-life of thiazides, and structural changes developing in distal tubule cells (cellular hypertrophy and hyperplasia) are avoided. To avoid hypokalemia caused by loop diuretics and thiazides, potassium-sparing diuretics can be added to the combination. However, since most of the patients with HF receive ACEIs or ARBs, it is recommended that the dose should be carefully titrated and potassium levels should be closely monitored.

8.6 What should be done in case of diuretic resistance?

Diuretic resistance is considered in the case of a lack of expected response to the standard diuretic therapy. Diuretic resistance may develop in 20-30% of patients with HF.

A reduction in the absorption of drugs in the gastrointestinal system, increased salt intake, the disruption of renal perfusion (low flow rate), a reduction in the secretion of diuretics from the kidneys, use of nonsteroidal anti-inflammatory drugs (NSAIDs), an increase in neurohormonal activity, hypertrophy and hyperplasia in distal tubules are the reasons for a reduction in the response to diuretics and for diuretic resistance.

In patients in whom the response to diuretic therapy reduces, the diet, dosage and administration of diuretics and concurrent use of other drugs should be reviewed. The patients' daily consumption of salt (<2 gr) and water intake (1-1.5 L) should be restricted. Use of NSAIDs reducing the efficacy of diuretics should be avoided. Electrolytes and renal functions should be monitored and fluid should be given in hypovolemic patients.

After all these causes are eliminated, increasing the diuretic dose can initially be favorable. Thus, the reduction in active secretion of loop diuretics into the tubule due to disrupted renal blood flow can be prevented. The dosing intervals of loop diuretics can be shortened due to their short half-life (2-3 times/day). Administering these agents with frequent intervals can prevent post-diuretic sodium retention. IV administration of loop diuretics increases bioavailability. Administering with continuous infusion can also be beneficial in improving diuretic resistance (Table 18).

In the DOSE Trial, administration of furosemide in bolus or continuous infusion and also low-dose or high-dose administration were compared in patients with acute decompensated HF (71). No difference was found between intermittent IV bolus administration and IV continuous infusion of furosemide. High-dose was observed to be superior in improving symptoms, weight loss and regression of congestions signs.

Table 18. Approach to diuretic resistance

Recommendations
Sodium and fluid restriction
Discontinuing NSAIDs
Volume replacement in hypovolemia
Increasing the dose and frequency of loop diuretics
Administration of diuretic therapy in IV bolus or continuous infusion
Combination of loop diuretics with thiazides or spironolactone
Adding dopamine to the treatment with the renal vasodilator dose (2-5 µg/kg/min)
Adding vasopressin antagonists to the treatment
Ultrafiltration

A combination of different diuretic drugs is another method in overcoming diuretic resistance (4). Concurrent administration of thiazides and potassium-sparing diuretics can be effective through sequential nephron blockade in diuretic resistance.

Dopamine infusion in low doses can be used to increase the efficacy of diuretics (3).

Adding vasopressin antagonists (tolvaptan, conivaptan) to the treatment can also be considered. Vasopressin antagonists, particularly used in the treatment of hypervolemic hyponatremia, are known to increase pure water elimination via the kidneys without showing a natriuretic or kaliuretic effect. In the EVEREST Trial, it was shown that routine tolvaptan administration to the patients with acute decompensated HF provided significant improvement in edema, body-weight and dyspnea although it had no effect on mortality and hospitalization (3, 4).

In order to reduce the fluid overload, ultrafiltration can be applied in patients who are unresponsive to the aforementioned precautions and administrations (3, 4).

ACEIs and ARBs decrease blood pressure and a reduction in blood pressure in HF increases the risk of diuretic resistance. However, due to their proven benefits in cardiovascular diseases, discontinuing these treatments or decreasing their doses should be the last resort.

8.7 How much can the diuretic dose be increased?

The ideal dose of diuretics to be used is not clear. The general approach is to adjust the dose according to the clinical condition of the patient.

Treatment with loop diuretics should be initiated at a low dose. The dose is titrated according to the diuresis response received and the symptomatic improvement. The initial dose of furosemide is 20-40 mg, PO or IV. Incrementing to high-doses may be required in patients with renal dysfunction. Even doses higher than 500 mg may be required depending on the condition

Table 19. Commonly used diuretic doses in heart failure

Diuretics	Initial dose (mg)	Routine daily dose (mg)	Maximum dose (mg)
Loop diuretics			
Furosemide	20-40	40-240	600
Bumetanide	0.5-1	1-5	10
Torasemide	5-10	10-20	200
Thiazides			
Hydrochlorothiazide	25	12.5-100	200
Metolazone	2.5	2.5-10	20
Indapamide	2.5	2.5-5	5
Potassium-sparing diuretics			
Spironolactone/eplerenone	12.5-25	25-50	100
Amiloride	5	10	20
Triamterene	50-75	100	200

of the patient. Switching to continuous IV infusion in these kinds of patients may be appropriate. Although the infusion dose of furosemide varies between 3 mg/hour and 200 mg/hour, generally 5-40 mg/hour is accepted as the sufficient dose. High-dose diuretic use should be avoided due to hypovolemia, hyponatremia, activation of renin angiotensin-aldosterone system and increase in the risk of mortality. Autotoxicity may develop in high doses. Total furosemide dose should be <100 mg in the first 6 hours and <240 mg in the first 24 hours.

Thiazides (25 mg hydrochlorothiazide, PO) and MRAs (25-50 mg spironolactone, PO) can be concurrently used with loop diuretics in HF patients with volume overload or diuretic resistance. The patients should be closely monitored in terms of hypovolemia, hyponatremia and hypo/hyperkalemia. Urine output and congestion signs should be closely monitored and the treatment should be planned accordingly.

Commonly used diuretic doses in HF are given in the Table 19 (3, 4).

9.0 Ivabradine, digoxin, hydralazine, and/or nitrate treatment – Yüksel Çavuşoğlu

9.1 Which one should be chosen in patients with heart rate of >70 bpm? Is it ivabradine or beta-blocker dose uptitration?

Elevated heart rate is associated with poor clinical outcomes in HF. The analyses of BB trials demonstrated that the mortality benefit of BB therapy correlated with the reduction in heart rate. Meta-analysis of 23 trials with BBs, including 19,000 cases, indicates that the benefits of BBs on mortality rates are strongly associated with a reduction in heart rate, rather than with dosage (72). The results of the SHIFT Study have shown that the reduction in heart rate achieved by adding ivabradine to the standard therapy including BBs, ACEIs/ARBs, MRAs, diuretics and digoxin in HF patients in sinus rhythm, with an EF <35% and a heart rate >70 b.p.m, significantly decreased cardiovascular death or HF hospitalization and HF-related death alone, HF hospitalization alone, all-cause hospitalization alone and cardiovascular hospitalization (23). These results show that reducing elevated heart rate in chronic HF-REF provided clinical benefit.

Beta-blockers are drugs which have proven to reduce mortality in HF in many major studies and, according to the guidelines, should be given to all patients (3). In patients in sinus rhythm with elevated heart rate (>70 b.p.m), ivabradine treatment should be added for heart rate control. In patients with elevated heart rate, the BB dose should primarily be up-titrated to the target or maximum tolerated dose. In patients with a heart rate >70 b.p.m despite the target or maximum tolerated dose of BBs, ivabradine should be added. In many studies, it is reported that the heart rate remains at >70 b.p.m in 50-70% of cases despite a BB use and that there is not a very good correlation between BB dose and heart rate control. It can be said that >50% of HF cases in sinus rhythm require ivabradine treatment considering that the rate of achievement of BB target dose is only 17% in real life or, despite the BB treatment, the heart rate is >70 b.p.m in many cases. BB and ivabradine treatments should not be considered alternatives for one another but complementary treatment forms. Also, European HF guidelines recommend ivabradine as an alternative of BBs in patients who have a contraindication for beta blocker therapy.

9.2 Which one should be chosen in a symptomatic patient? Ivabradine or digoxin?

The ESC guidelines for HF recommend ivabradine treatment primarily in cases with EF ≤35%, in sinus rhythm and at a heart rate ≥70 b.p.m who are symptomatic (NYHA Class II-IV) despite the maximum tolerated dose of BB, ACEI/ARB, MRA and diuretic treatment (3). Since the DIG Trial, which studied digoxin and demonstrated no mortality benefit, was conducted in the 1990s, the subjects in DIG had received only diuretics and ACEIs as a HF therapy (22). Therefore, the favorable efficacy of digoxin on hospitalizations, symptoms and quality of life has been proven in HF patients receiving ACEIs and diuretics. There is no evidence

as to whether digoxin provides an additional clinical benefit in patients receiving current modern therapy (e.g. BBs, ACEIs, MRAs, diuretics). However, ivabradine has been demonstrated to reduce the primary outcome of cardiovascular death or HF hospitalization and to reduce HF-related death alone, HF hospitalization alone, all-cause hospitalization alone and cardiovascular hospitalization significantly when added to the standard treatment comprised of BB, ACEI/ARB, MRA, diuretic and even digoxin (23). These results pointed out that ivabradine has a priority over digoxin. However, it should be kept in mind that that despite ivabradine treatment, digoxin can still be added to the ivabradine-based treatment in NYHA Class II-IV HF patients and concurrent use of these two drugs is not contraindicated.

9.3 What are the selection criteria for digoxin and ivabradine?

Ivabradine is indicated in patients with EF ≤35% and a heart rate ≥70 b.p.m who are still symptomatic (NYHA Class II-IV) despite maximum tolerated doses of BB, ACEI/ARB, MRA and diuretic treatment (3). As ivabradine exerts its effect through the inhibition of If channels located in the sinus node, the patient has to be in sinus rhythm (23). It is not used in AF. Therefore, the patient should be in sinus rhythm with a heart rate ≥70 b.p.m for the initiation of ivabradine treatment. These conditions are not applicable for digoxin. Digoxin can be used in sinus rhythm as well as in AF. There is no certain heart rate limit for digoxin use. Digoxin is known to be a quite effective drug in ventricular rate control in AF. Therefore, its use in AF is particularly recommended for rate control. There is a limitation of digoxin use in chronic renal failure due to intoxication. Ivabradine use is effective and safe in these cases.

On the basis of this information, in patients with EF ≤35%, in sinus rhythm and who are still symptomatic despite the maximum tolerated doses of BB, ACEI/ARB, MRA and diuretic treatment, it is appropriate to initiate ivabradine primarily if the heart rate is ≥70 b.p.m, and digoxin may be chosen in patients with a heart rate <70 b.p.m. In patients with a heart rate ≥70 b.p.m and uncontrolled symptoms despite the administration of ivabradine, adding digoxin to the treatment should be considered. Ivabradine should be the first choice in patients with chronic renal failure and a heart rate ≥70 b.p.m. In HF with AF, digoxin can be started in symptomatic cases, particularly those with a fast ventricular response, regardless of heart rate. However, it should be noted that digoxin can reduce heart rate with concurrent use of BBs and/or ivabradine in bradycardic patients (heart rate <60 b.p.m.) and its use should be avoided in those with a heart rate <50 b.p.m.

9.4 What is the target heart rate for ivabradine?

The results of the SHIFT Study support the fact that there is a 3% increase in the risk of death and HF hospitalization for every 1 b.p.m increase in heart rate (23). In cases whose heart rate reduces by >10 b.p.m with ivabradine treatment, primary outcomes of cardiovascular death or HF hospitalization are observed to reduce significantly compared to the less reduced or non-reduced cases. In the same study, optimal heart rate for the reduction of primary outcomes was found to be 55-60 b.p.m. (23). In the meta-analysis of 23 BB studies, it has been reported that mortality benefit was significant in patients whose heart rate decreases below 70 b.p.m with BB treatment (73). These results support that a heart rate of 55-65 b.p.m. is the ideal target range with ivabradine treatment (Table 20).

9.5 Should a loading dose of digoxin be administered? When and how should it be given?

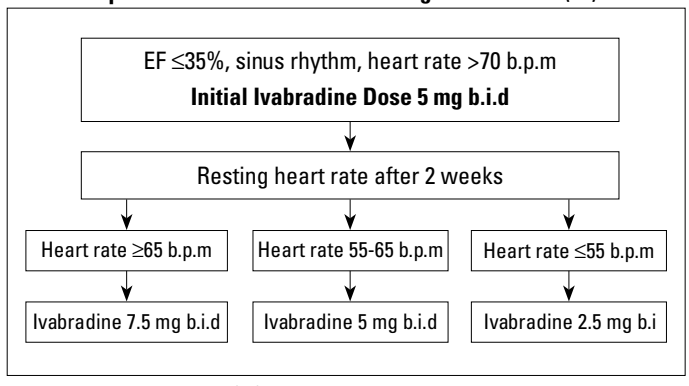
There is no rationale for the loading dose of digoxin in patients who have clinically stable HF. 0.125 or 0.25 mg/day is recommended as the initial and maintenance doses (4). 0.125 mg/day or 0.125 mg every other day is recommended in mild-moderate renal dysfunction, advanced age (>70 years) or patients with a low body weight. Post-hoc analyses of the DIG Trial support that there is mortality benefit in patients with plasma digoxin levels of 0.5-0.9 ng/mL, there is no effect on mortality in patients with levels of 0.9-1.1 ng/mL, and higher plasma levels (≥1.2 ng/mL) are associated with an increase in death risk (22, 74). Therefore, if it can be measured, dose adjustment can be performed by monitoring the plasma levels of digoxin.

The most important condition for loading dose of digoxin is acute HF presenting with rapid ventricular rate response of AF. In this case, if there is hemodynamic instability, sinus rhythm should be restored with cardioversion. If there is no hemodynamic instability and the rapid ventricular rate of AF is considered to be controlled immediately, IV digoxin can be administered. The use of BB for rate control in this setting may worsen acute HF manifestation. IV digoxin administered as 0.25 mg or 0.5 mg by considering the patient's body weight, age, renal functions and whether or not the patient is under digoxin treatment can provide rate control within 30-60 minutes and additional oral digoxin tablets not exceeding the total dose of 0.75-1.0 mg. can be given, if necessary.

9.6 How should the digoxin be administrated according to the creatinine level?

Digoxin is mainly excreted by the kidneys. The risk of intoxication increases in patients with renal dysfunction. Therefore,

Table 20. Up-titration of ivabradine according to heart rate* (23)



*Adapted from SHIFT Study (23)

in patients in which digoxin treatment is considered, the decision for the initiation of digoxin treatment should be based on plasma creatinine levels or GFR and the assessment of the risk/benefit ratio is required. In assessing the renal functions, GFR gives more accurate information. Even though creatinine levels are normal, particularly in patients with advanced age, GFR may be found to be significantly low. It would therefore be more appropriate to decide on the functions of the kidneys with GFR in elderly patients. In patients with mild-moderate renal dysfunction, it is recommended to reduce the digoxin dose by half or to 1/4 of the dose and to repeat the measurement of plasma levels in intermittently, if possible. Recommended digoxin doses considering body weight and GFR are given in Table 21 (75). Although only 0.25 mg oral formulation is available in our country, 0.125 or 0.0625 mg formulations are available in some countries for low dose convenience.

Table 21. Recommended-doses of digoxin according to body weight and GFR* (75)

Body Weight - GFR, mL/min	Digoxin dose, mg/day
45-50 kg - ≤60	0.0625
45-50 kg - >60	0.125
51-60 kg - ≤45	0.0625
51-60 kg - 46-110	0.125
51-60 kg - >110	0.25
61-70 kg - ≤35	0.0625
61-70 kg - 36-110	0.125
61-70 kg - >110	0.25
71-80 kg - ≤21	0.0625
71-80 kg - 21-80	0.125
71-80 kg - >80	0.25
81-90 kg - ≤10	0.0625
81-90 kg - 11-70	0.125
81-90 kg - >70	0.25

GFR - glomerular filtration rate
*Adapted from DiDomenico RJ et al (75).

9.7 Is there a rationale for skipping digoxin doses 2 days a week?

Digoxin administration in the DIG Trial is 0.25 mg/day (22). There is no rationale for skipping a dose 1 or 2 days a week, which is a common clinical practice almost solely in our country. In patients who have a concern for the development of digoxin intoxication, the ideal approach is to adjust the oral dose by measuring plasma digoxin levels. If there is no opportunity to measure the plasma digoxin levels, 0.125 mg. or 0.0625 mg. every day or every other day can be given in patients with mild-moderate renal dysfunction, low body weight or advanced age (>70 years).

9.8 Do hydralazine and/or nitrate provide clinical benefit in Whites?

Clinical studies show that H-ISDN combination reduces mortality, HF hospitalizations and improves ventricular function, symptoms and exercise capacity. There is strong evidence regarding the mortality benefit of H-ISDN, particularly in African-Americans. In the V-HeFT-I Trial (45), improvement was observed in exercise capacity, EF and all-cause mortality with H-ISDN treatment added to the diuretic and digoxin treatment. However, in V-HeFT-II (46) with enalapril, all-cause mortality was found to be significantly lower than H-ISDN (18% and 25%, p=0.016). The A-HeFT Trial (25), including African-American subjects, was terminated early due to a 43% (p<0.02) reduction in mortality and 33% (p<0.001) reduction in hospitalization when H-ISDN was added to the treatment of HF in patients with NYHA Class III-IV and reduced EF who were receiving diuretics, digoxin, ACEIs (ARBs), BBs and spironolactone. V-HeFT-I and V-HeFT-II are trials including African-American and White subjects. Recently published studies show that H-ISDN added to the ACEI/ARB treatment reduced all-cause mortality by 35% (p=0.04) and all-cause mortality/HF hospitalization by 28% (p=0.03) and significantly improved cardiac index and systemic vascular resistance in Whites (76). Although these results strongly support the clinical benefits of H-ISDN, particularly in African-Americans, they also support the fact that H-ISDN may provide clinical benefits in Whites who are unresponsive to standard treatments or who have contraindication/intolerance to standard drugs.

9.9 Can nitrate alone be used instead of hydralazine+nitrate combination?

Hydralazine and ISDN are vasodilator agents with arterial vasodilator action and venodilator action, respectively. There is no H-ISDN combination in our country. In the H-ISDN combination, both arterial and venous vascular dilation are achieved. Thus, preload and afterload reduce as a result from a decrease in systemic and venous vascular resistance. Although nitrates show venodilator effect prominently, they also have arterial vasodilator properties. Although H-ISDN combination has been evaluated in most of the HF clinical trials and clinical benefits have been proven with H-ISDN combination (25, 45, 46), in the absence of H-ISDN combination, use of nitrate alone can be considered to provide similar clinical benefit, at least partially. Furthermore, some of the previously published studies have shown that administration of ISDN alone in HF improved symptoms and exercise tolerance (77, 78). Despite the lack of strong evidence, it seems reasonable to use nitrate alone when necessary until the H-ISDN combination is available in our country.

9.10 Does nitrate tolerance develop in nitrate use? What should be done in this case?

One of the most important issues in nitrate use is the development of nitrate tolerance. It is observed in all nitrate forms. Tolerance disappears after a nitrate-free period of 10-12 hours. Nitrate tolerance mainly affects systemic resistant vessels rather than large vessels. Development of nitrate tolerance is

therefore important in HF. Development of partial or full tolerance is observed in the use of both ISDN and isosorbide-5-mononitrate. ISDN is administered as 20-40 mg, 3-4 times daily in HF. In clinical practice, a nitrate-free period of 10-12 hours is recommended. Therefore, 3-dose administration at 08:00, 13:00 and 18:00 or 3-dose administration every 6 hours is ideal for providing a nitrate-free period. Tolerance does not develop in the use of isosorbide-5-mononitrate once daily; however, it develops if 2 doses are received at 12-hour intervals. Therefore, use of extended-release isosorbide-5-mononitrate once daily allows for a sufficient nitrate-free period with no tolerance. Generally, the ISDN dose used in HF studies is 120-160 mg/day (25, 45, 46).

9.11 How can we overcome the headache problem during nitrate use?

One of the common side effects observed with nitrate use is headache. Initiating the treatment with a short-acting nitrate (ISDN) is therefore recommended. If headache develops, uptitration to desired doses by starting with a quarter of the dose and doubling the dose every 2-3 days result in the development of tolerance to headache. In severe cases, powdering the ISDN tablet, taking a pinch of the ISDN dose and incrementing the amount generally help to overcome headache problem.

10.0 Drug use in pregnant and/or breastfeeding women – Mehdi Zoghi

10.1 Which drugs can be used in pregnant women?

Treatment principles in acute and chronic HF in pregnant women are the same as the cases of general HF population except for the requirement to be cautious about the drugs with teratogenic effects on the fetus. In this context, ACEIs, ARBs and MRAs are teratogenic and should not be used during pregnancy. Hydralazine and/or nitrates can be used instead of ACEIs/ARBs to reduce afterload. If a significant reduction is observed in LVEF after the discontinuation of RAAS blockers, the risk of pregnancy should be reviewed. If these groups of drugs had been received in the first trimester, they should immediately be discontinued, and the condition of the fetus should be examined with fetal USG. Mechanical left ventricular support devices or heart transplantation (4%) may be required in patients with peripartum cardiomyopathy resistant to drug treatment (79).

Although our knowledge on BBs use in pregnancy is obtained from evidence in hypertensive pregnant women, beta-1 selective BBs are recommended. Metoprolol has much more evidence in pregnancy compared to any other beta blockers and can be used more safely. Atenolol use is not recommended. Although digoxin can also be used in pregnancy safely, it is not among the initially preferred drugs, as has been used in general HF population. Loop diuretics can be given in pregnant women with prominent symptomatic pulmonary edema and peripheral edema (79). If indicated, dopamine and levosimendan can also be used in pregnant HF women.

10.2 Which drugs can be used in breastfeeding women?

The amount of ACEIs excreted into breast milk is very low. However, ACEIs that have been proven to have a safe profile in clinical trials in breastfeeding women (enalapril, captopril or benazepril) should be preferred (Table 22). There is no enough data regarding the safety of ARBs. Furosemide can reduce milk production. Metoprolol succinate extended-release is a BB with

Table 22. Drugs and their categories in pregnancy and breastfeeding

Drug	TGA pregnancy category	Compatibility with breastfeeding
Enalapril	D	Compatible
Ramipril	D	Caution, insufficient data
Captopril	D	Compatible
Perindopril	D	Caution, insufficient data
Candesartan	D	Avoid, insufficient data
Valsartan	D	Avoid, insufficient data
Metoprolol	C	Compatible
Carvedilol	C	Caution, insufficient data
Nebivolol	C	Caution, insufficient data
Spironolactone	B3	Compatible
Furosemide	C	Caution, insufficient data
Ivabradine	D	Caution, insufficient data
Digoxin	A	Compatible
Nifedipine	C	Compatible

TGA - therapeutic goods administration
A: Controlled human studies show no risk; B: No evidence of risk in studies; B3: No evidence of risk in limited number of studies; C: Risk can not be ruled out; D: Positive evidence of risk

less excretion into breast milk and with more clinical research compared to any other BBs. Oral digoxin preparations are among the drug groups which can be used safely (79, 80).

11.0 Controversial issues in drug therapy in HF – Mehmet Birhan Yılmaz

11.1 Do omega-3 PUFA and statin treatments provide clinical benefit?

The efficacy of omega-3 PUFA treatment in chronic HF has been evaluated in the GISSI-HF Trial (81). In this trial, 6975 patients with NYHA Class II-IV symptoms were randomized to receive 1 g omega-3 PUFA or placebo. A slight but significant reduction was observed in the composite outcome of all-cause mortality and death or HF hospitalization (hazard ratio [HR] 0.91 [95.5% CI 0.833-0.998], p=0.041 for mortality). Additionally, in a sub-group analysis, it has been demonstrated that a slight improvement was provided in ejection fraction with this treatment (82). Omega-3 PUFA treatment can therefore be recommended in patients with chronic HF.

Statin treatment is recommended in the guidelines as Class I indication in patients with a history of previous acute myocardial infarction (AMI) or ACS (Stage A) in order to prevent the development of symptomatic HF and CV events. This indication is a prophylactic treatment. In patients with established HF, initiating statin for only HF treatment has no benefit. Despite the favorable findings in observational studies and post-hoc analyses, in two major trials conducted with rosuvastatin, the efficacy of statin treatment in patients with HF-REF has been demonstrated to be neutral. The guidelines therefore clearly state that adding statin to the standard treatment has no benefit on Stage B and C chronic HF and it is recommended as Class III indication with level of evidence "A" with the exception of the indications where its use is mandatory.

11.2 Do statins have a benefit in HF patients with hyperlipidemia and CAD?

Atherosclerotic disease is known to be an important and common factor in the development of HF. Aggressive treatment of hyperlipidemia with statins reduces the risk of HF development in high-risk patients. Statin treatment should therefore be initiated in the presence of compelling indications in Stage A patients defined as a group with a high risk for HF development in whom the symptomatic HF clinic has not yet developed (4). It should be kept in mind that this is a prophylactic treatment for the development of HF. As a treatment solely for HF, statins have no benefit in Stage C and D patients with symptomatic HF (particularly HF-REF) (83). On the other hand, a recent meta-analysis evaluating the results of CORONA and GISSI-HF trials reported that rosuvastatin therapy might have a slight favorable effect regarding the prevention of MI in ischemic HF (84). However, in HF patients with CAD, statins should not be discontinued except significant side effects.

11.3 Does ASA reduce the benefit of HF-specific drug therapy?

Aspirin (or OAC) therapy (even in low doses) has no benefit in patients with HF, particularly HF-REF. Furthermore, due to a high risk of bleeding, their use can be restricted except for compelling indications. On the other hand, because of the pharmacokinetic pathway, it may limit the nephroprotective effects of ACEIs and BBs (the effect of urodilatin is included). However, it should be kept in mind that other NSAIDs except Aspirin (including COX-2 inhibitors) have unfavorable effects in patients with HF via the abovementioned action, which is also emphasized in the guidelines (4). Despite the belief that ASA might limit the effects of HF-specific drug therapy, this has not been confirmed in the analyses of major HF trials. ASA use should be limited to compelling indications, and liberal use might be avoided.

11.4 Does warfarin therapy have a place in patients with HF in sinus rhythm?

In a randomized trial conducted in patients with HF-REF in sinus rhythm comparing warfarin and aspirin therapy, no difference has been observed regarding efficacy; however, bleeding has been reported more frequently in the warfarin arm. Therefore, warfarin therapy has no benefit in patients with HF-REF in sinus rhythm (patients should be closely monitored regarding paroxysmal AF). On the other hand, in a study examining the recent CORONA and GISSI-HF collective dataset, it was suggested that a subgroup could be determined in which anticoagulant treatment might have been beneficial even if there was no AF in the high-risk patients with HF-REF (85). This expectation is being tested in the ongoing COMMANDER-HF Trial regarding the possible positive effect of NOAC therapy (69).

11.5 Should warfarin be administered in case of severe ventricular dysfunction?

The beneficial effect of oral anticoagulant (OAC) therapy in severe left ventricular dysfunction is still controversial and uncertain. Hypothetically, since there might be a patient group which may derive potential benefit from OAC therapy, all antiaggregant-anticoagulant discussions are settled to refer to this hypothesis in the literature. It is a subject evaluated within the context of sub-group analysis as evidence. In the sub-group analysis of the WARCEF Trial, the risk of new ischemic cerebrovascular event has been found to be high in patients with EF <15% compared to other HF-REF patients (86). In an analysis performed recently, the risk of stroke was shown to be 60% higher in HF-REF patients in sinus rhythm with NYHA Class III-IV symptoms than patients with NYHA Class II symptoms (85). Hence, theoretically, anticoagulant therapy may be beneficial in HF-REF patients with low EF and high NYHA class. However, in this group with high risk of cerebrovascular event, it should be kept in mind that risk of bleeding is high in particular considering the age of the patient (87). It is therefore not possible to make a clear and general recommendation in this regard.

12.0 New drugs in heart failure

12.1 ARNI (LCZ696) – Mehmet Birhan Yılmaz

Angiotensin receptor neprilysin inhibitor is a molecule which ends the reign of invincible ACEI (enalapril) therapy regarded as the backbone of chronic HF-REF treatment (17). ARNI (LZC696) is a chemical compound of valsartan/sacubitril salt. In this molecule, valsartan is an ARB and sacubitril is a neprilysin inhibitor. Neprilysin inhibitors are drugs inhibiting the enzyme responsible for the degradation of some vasoactive molecules (including bradykinin, angiotensin-2) mainly atrial natriuretic peptide (ANP). Angiotensin-2 levels increase with their single use (88). Therefore, by combining with ARBs or ACEIs, the effects of angiotensin-2 should be inhibited. Since their combination with ACEIs has been observed to increase the risk of angioedema significantly in the previous studies, their use with ACEIs has been abandoned. Their concurrent use with ARBs is the safest combination possible. Thus, while ARNI blocks the unfavorable effects of RAAS axis on one hand, it provides a double benefit with the prolonged effect of molecules with favorable effects generated by neprilysin inhibition on the other hand. Therefore in the PARADIGM-HF Trial, ARNI reduced CV mortality or HF hospitalizations by 20%, CV mortality alone by 20%, HF hospitalizations alone by 21% and all-cause mortality alone by 16% in HF-REF patients with NYHA Class II-IV (NYHA IV was represented in a very low number) compared to high dose enalapril treatment (17). Angioedema, the greatest concern, was reported anecdotally. It is noteworthy that substitution therapy was shown to be effective in HF-REF instead of usual add-on therapy. According to the results of the PARADIGM Trial, in HF-REF patients with appropriate indication, it seems that ARNI therapy instead of ACEI (or ARB) will be strongly recommended in guidelines. However, there are matters that still need clarification. For example, ARNI has not been tested yet in post-MI patients. Furthermore, its use in patients who are ACEI/ARB-naïve or with Stage B asymptomatic HF is not clear regarding evidence-based medicine. Its possible use in patients with HF-PEF is still under investigation (PARAGON-HF).

12.2 Tolvaptan – Yüksel Çavuşoğlu

Vasopressin (antidiuretic hormone) levels increase in HF. This increase is much more significant in HF patients with NYHA Class III-IV (89). Non-osmotic vasopressin release caused by an increase in angiotensin II levels and baroreceptor activation, and also reduction in vasopressin degradation due to liver/kidney dysfunction are the mechanisms responsible for the increase in vasopressin levels in HF (90). Vasopressin causes free water retention via V2 receptors in renal collecting ducts. It also causes vasoconstriction, inotropy and hypertrophy via V1a receptors found in vascular smooth muscle and myocardium. Excessive water retention increases intravascular and extravascular congestion. This worsens hypervolemic hyponatremia particularly in hyponatremic cases. When the hyponatremia limit is considered <135 mEq/L, it is reported that 8-27% of the cases admitted to the hospital with HF have hyponatremia. Hyponatremia, especially plasma sodium level <130 mEq/L, is associated with mortality, rehospitalization, longer hospital stay and higher cost (91).

Vaptans are agents exerting effect by increasing free water elimination from kidneys. The vaptans used currently are tolvaptan and conivaptan. Tolvaptan is an oral V2 selective vasopressin receptor blocker and conivaptan is an IV V1a and V2 non-selective vasopressin receptor blocker. Tolvaptan is commercially available in our country and its main indication is hypervolemic hyponatremia. The EVEREST Study showed that in hospitalized patients for acute decompensated HF with or without hyponatremia, adding tolvaptan to the standard therapy has no effect on mortality or HF hospitalizations; however, it provided significant improvement in dyspnea, edema, body weight and hyponatremia compared to the standard treatment (92). Recent subgroup analyses supported that it has a significant benefit in reducing mortality or cardiovascular hospitalization in hyponatremic cases (93). There are randomized, double-blind trials showing that tolvaptan increases the amount of urine output and improves congestion in cases resistant to diuretic treatment (93). Studies show that the need for high dose diuretic use reduces with tolvaptan use and kidney functions are maintained. In cardiorenal syndrome, it is reported to be beneficial by increasing the urine output without worsening renal functions. Therefore, tolvaptan has an indication in the treatment of HF associated with congestion in Japan. It is indicated in the treatment of hypervolemic hyponatremia in many countries, including Turkey as well. However, besides hyponatremia, tolvaptan should be considered in cardiorenal syndrome and severe congestion resistant to diuretics and can decrease the need for ultrafiltration.

12.3 Aliskiren – İbrahim Sarı

ACEIs (or ARBs), BBs and MRAs which are used as standard drugs of HF suppress neurohormonal overactivity by blocking the final steps of RAAS. However, they cause an increase in compensatory renin secretion. Renin inhibitors prevent angiotensin-I formation from angiotensinogen by binding to the active site of renin molecule thereby showing its effect in the first step of RAAS cascade. It is therefore believed that renin inhibition may have an additional benefit in the treatment of HF. Aliskiren is an orally active direct renin inhibitor with a non-peptide structure.

To date, there are three trials examining the use of aliskiren in the treatment of HF (Table 23). In the ALOFT Trial which is the first of these trials, it has been shown that aliskiren, a direct renin inhibitor, added to the therapy of NYHA Class II-IV HF patients who are treated with ACEIs (or ARBs) and BBs provided significant additional neurohormonal benefits by reducing N-terminal pro-brain natriuretic peptide (NT-proBNP) and urinary aldosterone levels (94). In the ASTRONAUT Trial, adding aliskiren in the median 5th day to the current therapies of hospitalized patients due to worsening chronic HF (85% of the patients were on ACEI and/or ARB) revealed similar results with the placebo concern-

Table 23. Clinical trials examining aliskiren in HF

	ALOFT	ASTRONAUT	ATMOSPHERE
Patient characteristics	Chronic HF	During acute HF hospitalization, EF <40%, BNP ≥400 or NT-proBNP ≥1600 pg/mL	Chronic HF, EF <35% and increased BNP
Number of patients	302	1639	7041
Mean age	55	65	?
Functional class	II-IV	II-IV	II-IV
Trial duration	3 months	12 months	1 year and longer
Treatment arms	Aliskiren or placebo (1:1)	Aliskiren or placebo (1:1)	Aliskiren or enalapril or aliskiren+enalapril (1:1:1)
Primary end-point	Change in the NT-proBNP level	CV mortality or HF hospitalization in months 6 and 12	CV mortality or HF hospitalization
Result/comment	Significant reduction is observed in NT-proBNP, BNP and urinary aldosterone levels in the aliskiren group. Plasma renin activity demonstrated more reduction in the aliskiren group	Similar to placebo. While placebo is better in 12-month follow-up in diabetics, aliskiren is better in non-diabetics; hypotension and impairment in renalfunctionoccur more frequently in the aliskiren group	Patient enrollment is over. The results are expected to be announced at the end of 2015

ing primary end-point (95). Finally, the ongoing ATMOSPHERE Trial, the results of which are expected to be announced soon, aims to evaluate the effects of enalapril alone, aliskiren alone or the combination of these drugs on cardiovascular (CV) mortality and CV hospitalizations in 7000 patients with systolic HF (96).

Aliskiren is mentioned neither in ESC guidelines 2012 nor ACCF/AHA guidelines 2013 for the treatment of HF. In conclusion, in the light of current knowledge, aliskiren has no place in the treatment of HF as an alternative or additional therapy to ACEIs (or ARBs). However, the ATMOSPHERE Trial, the largest trial in this regard, will elucidate this matter.

12.4 Non-steroidal MRAs – Ahmet Ekmekçi

Mineralocorticoid receptors (MR) are mineralocorticoid and glucocorticoid dependent intracellular steroid receptors. MRs are localized in a number of tissues, mainly in the kidneys and heart. Eplerenone and spironolactone (and its metabolite potassium canrenoate) are MR antagonists (MRA) which are used in current clinical practice. Spironolactone is a non-specific MRA but show high-affinity for MR and because of structural similarity with progesterone, it has also a weak interaction with progesterone, androgen, and glucocorticoid receptors. Eplerenone also comprises a steroid component, show high affinity for MR and, although minimal, it can also act on progesterone and androgen receptors. There are also non-steroidal MRAs such as Finerenone and BR4628 which are still under investigation. These drugs have similar effects on MR but due to their non-steroidal structures, side effects such as impotence, gynecomastia and menstrual irregularity are either not present or extremely low. Furthermore, since their affinity on cardiac MR is much higher than that of kidneys, general and significant side effects of MRAs such as hyperkalemia are also low. In a study, fineronone reduced hemodynamic stress biomarkers similarly to spironolactone, however, caused less hyperkalemia in patients with reduced LVEF and moderate renal dysfunction (97, 98). Comparison of available MRAs and fineronone, a promising molecule subject to ongoing clinical trials, is given in the Table 24.

13.0 What is the role of natriuretic peptides in the management of heart failure therapy? – Mehmet Birhan Yılmaz

The fact that natriuretic peptides are quantitative biomarkers of myocardial wall stress leads to the consideration of the place of these biomarkers in disease management. Primarily, there are at least two published evidences on the prevention of HF development and its treatment. As shown in both PONTIAC (99) and STOP-HF (100) Trials, identification, close monitoring and treatment of asymptomatic patients in high-risk population whose natriuretic peptide levels are slightly above the limit will improve the results. Therefore, natriuretic peptides can find a place in the diagnosis and treatment of HF. On the other hand, studies performed regarding the role of HF treatment managed with the guidance of natriuretic peptides in Stage C and D patients have given different and inconsistent results. Therefore, chronic HF treatment with the guidance of natriuretic peptides is shown as

Table 24. Comparison of available MRAs and fineronone

	Finerenone (BAY94-8862)	Spironolactone	Eplerenone
Chemical group	Non-Steroidal	Steroidal	Steroidal
Mechanism of action	Competitive MRA	Competitive MRA	Competitive MRA
MR affinity	+++	+++	+
MR selectivity	+++	+	+++
Inhibition of nongenomic MR effect	Unknown	No	Yes
Initiation of activation and loss of effect	Unknown	Slow	Rapid
Bioavailability	Unknown in humans, 94% in rats	60-90%	Absolute bioavailability is not known
Binding to proteins	Unknown	Binding by 90%	Binding by 50%
Metabolism	Unknown	Hepatic, active metabolite	Hepatic, inactive metabolites by CYP3A4
Half-life	Unknown	1-2 hours	4-6 hours
Elimination time of the drug and its metabolites	Unknown	10-35	4-6 hours

Class IIa indication in the guidelines.

In a recent meta-analysis (101), natriuretic peptide guidance has been found to be effective in reducing all-cause mortality in patients younger than 75 years of age [hazard ratio = 0.62 (0.45–0.86); P = 0.004] in the outpatient management of chronic HF. This effect is not the same in patients above 75 years of age. On the other hand, natriuretic peptide guidance has been found to be effective independent of age in terms of reducing HF hospitalizations. Current problems are the use of either absolute rank or percentile rank, the sensitivity and precision of the method used in evaluating the reference peptide, lack of clarity of what will change in a patient receiving the highest-dose of prognosis-modifying therapy, other confounding factors (obesity, etc.) and accompanying diseases. Solving all of these problems at once does not seem to be possible. However, it should be kept in mind that natriuretic peptide guidance can affect prognosis favorably in patients whose drugs such as ACEIs, ARBs, BBs or MRAs have not been up-titrated to the highest dose yet.

14.0 Which drugs adversely affect the clinical picture and should be avoided? – Ahmet Ekmekçi

Care should be taken regarding three main groups of drugs in patients with HF including drugs with negative inotropic effect, drugs causing sodium retention and drugs with directly cardiotoxic effects (102).

Non-steroidal anti-inflammatory drugs — The use of non-steroidal anti-inflammatory drugs are recommended to be avoided in HF due to causing the worsening of HF independent of ejection fraction and causing renal dysfunction as well as reducing the beneficial effects of angiotensin-converting enzyme inhibitors (ACEIs) and diuretics. Observational data indicates that NSAID use increases mortality. This is also true for COX-2 selective inhibitors. Although aspirin is indicated and provide clear clinical benefit in patients with cardiovascular disease, there is not enough data regarding benefit-risk ratio in patients with HF not accompanied by cardiovascular disease (103).

Calcium channel blockers (CCBs) — Due to their negative inotropic effect, the use of CCBs, particularly the non-dihydropyridine group of CCBs (verapamil, diltiazem), should be accepted as contraindicated in patients with HF. However, in clinical trials conducted with amlodipine, a vasoselective agent in the dihydropyridine group, it has been observed that amlodipine has neutral effect in mortality and morbidity. Therefore, when CCBs should be used in other indications such as angina or hypertension, only amlodipine and felodipine can be used in patients with HF (102, 104).

Antidepressants — Depression is associated with poor clinical outcomes including an increase in mortality in patients with HF. Therefore, it should be treated. Tricyclic antidepressant (TCA) drugs are not recommended due to poor end-points in patients with systolic HF. However, in an analysis of randomized, controlled trials, it has been observed that there was no difference in terms of HF, myocardial infarction, stroke or cardiovascular mortality between TCAs and selective serotonin reuptake inhibitors, but other cardiovascular side effects such as palpitation were higher with TCAs (105).

Oral hypoglycemic agents — Thiazolidinediones including pioglitazone should not be used as they cause fluid retention. Although metformin is a less preferred agent by clinicians due to causing lactic acidosis, it can be used in clinically stable HF patients (106).

Antiarrhythmic agents — Some of antiarrhythmic drugs are not preferred due to their negative inotropic effects, Class I and III agents (such as ibutilide and sotalol) due to their proarrhythmic effects and again ibutilide, sotalol, and dofetilide due to causing QT prolongation and torsades de pointes (102).

Chemotherapeutic agents — Cardiotoxic drugs such as an-

thracyclines, high-dose cyclophosphamide, trastuzumab, bevacizumab, paclitaxel and interferon should be used under close follow-up.

15.0 Which drugs should be used with caution to avoid drug-drug interaction? – Ahmet Ekmekçi

Drug-drug interaction is an important cause for morbidity and mortality in patients with HF. Generally, drugs can be affected by pharmacodynamic drug interactions (Table 25). For example, digoxin, amiodarone, warfarin and BBs are metabolized by CYP 2D6. The risk of severe hyperpotassemia increases with concurrent use of ACEIs, ARBs, MRAs and BBs (107). The risk of digoxin toxicity increases in the presence of hypokalemia. The risk of bleeding increases with concurrent use of warfarin, aspirin, clopidogrel, ticagrelor, and prasugrel. With the use of some antiarrhythmics in combination, QT prolongation and life-threatening arrhythmias can be observed. Some diuretics used in combination cause electrolyte imbalance. Concurrent use of nitrates, alpha-blockers, BBs, ACEIs, diuretics, sildenafil, and CCBs increases the risk of hypotension. Concurrent use of amiodarone, BBs, digoxin, verapamil, diltiazem, sotalol, and propafenone is associated with the risk of bradycardia (107, 108).

In patients with volume overload; drug absorption, distribution and clearance may change due to intestinal edema, hepatic congestion, and renal failure. The effect of warfarin may increase in acute conditions. The digoxin clearance reduces in the setting of acute decompensation and requires close monitorization. The effect of digoxin is increased by amiodarone, verapamil, diltiazem, propafenone, captopril, carvedilol, spironolactone, macrolides, and triamterene and decreased by salbutamol, sucralfate and rifampin. It is well-known that more than 70 drugs change the efficacy of warfarin. The effect of warfarin is increased by amiodarone, quinidine, cimetidine, allopurinol, cephalosporins, and metronidazole and decreased by cholestyramine, barbiturates, and phenytoin. In patients receiving PDE-5 inhibitors, regular or even intermittent use of nitrates may cause severe and lethal hypotension. In patients who will receive nitrates, sildenafil and tadalafil should be discontinued prior to 24 and 48 hours, respectively (109).

16.0 Drug therapy in atrial fibrillation – Ahmet Ekmekçi

16.1 Does rhythm control provide clinical benefit in HF?

Atrial fibrillation is observed in 13-27% of patients with HF depending on the severity of HF (110). In AF trials regardless of HF, no clear beneficial effect of pharmacological rhythm control has been demonstrated on survival. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and RAte Control vs Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) Trials, no superiority of rhythm control over rate control in terms of cardiovascular mortality and morbidity has been found (111, 112).

In the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) Trial including HF patients with AF, rate or rhythm control have been observed to cause no difference regarding cardiovascular mortality or any cause mortality, worsening of HF or stroke in patients with congestive HF symptoms, AF, and LVEF $\leq$ 35% in a 37-month follow-up (113). Rhythm control is recommended only in patients who are symptomatic despite sufficient rate control (114, 115). Results of an analysis from the AFFIRM Trial have suggested that unfavorable effects of antiarrhythmic drugs used in rhythm control reduce the benefits provided by sinus rhythm (116).

16.2 What should the drug selection be in rate control?

Ensuring rate control in patients with AF requires adjusting the dosing frequency of the drugs, use of various drug combinations and frequent medication changes (117-119).

Commonly used drugs for rate control are BBs, non-dihydropyridine calcium channel antagonists, digoxin, and amiodarone. These drugs are used alone or in combination as needed.

Table 25. Possible adverse effects which can be observed with concurrent use of common drugs in HF are given in the table below

Drug-drug combination	Severity	Potential adverse effect
ACEI + Diuretic (loop or thiazide)	Moderate	Postural hypotension
ACEI + Potassium-Sparing diuretic	Major	Hyperkalemia
Phenprocoumon + Spironolactone	Moderate	Decreased anticoagulant effectiveness
Aspirin (acetylsalicylic acid) [low dose] + LMWH	Moderate	Increased risk of bleeding
Antidiabetic agent +β-Adrenoceptor Antagonist	Moderate	Decreased diabetic control
Aspirin (low dose) + Clopidogrel	Minor	Increased risk of bleeding
Clopidogrel + Torasemide	Moderate	Torasemide toxicity
LMWH + Phenprocoumon	Major	Increased risk of bleeding
ACEI + Potassium	Major	Hyperkalemia
Amiodarone + Phenprocoumon	Moderate	Increased risk of bleeding

ACEI – angiotensin-converting enzyme inhibitor; LMWH – low molecular weight heparin

BBs are the most effective agents for rate control (113). BBs are known to reduce mortality and morbidity in patients with HF and therefore their use is recommended as Class IA indication in HF guidelines (120). Another advantage of BBs is that they can control heart rate during both rest and exercise (121).

In AF patients with chronic systolic HF, digoxin can also be preferred for rate control. However, while digoxin reduces ventricular rate during rest, it is not effective on rate control during exercise (121, 122). Use of digoxin is difficult due to its narrow therapeutic range and high drug interaction. The most common side effects are ventricular arrhythmia, atrioventricular block and sinus pause and they are all dose-dependent. Concurrent use of BBs and digoxin provides better results than their single use in terms of providing rate control, reducing symptoms and improving ventricular functions (123).

Amiodarone is a less effective antiarrhythmic agent in rate control. It is recommended in cases where ventricular rate control cannot be provided by BBs and digoxin in patients with chronic HF (122). However, it can be used to ensure acute ventricular rate control intravenously or in high doses orally (124).

Non-dihydropyridine calcium channel antagonists (verapamil, diltiazem) should not be used in patients with systolic HF due to their negative inotropic effects. However, they can be used in HF-PEF with AF for rate control (125).

16.3 Does beta-adrenoceptor gene polymorphism have an effect on rate control?

Beta-blocker response varies from patient to patient. The treatment should therefore be planned individually. One of the reasons why efficacy of BBs varies from patient to patient is β1 adrenoceptor Arg389Gly gene polymorphism. Cyclic adenosine monophosphate synthesis reduces with substitution of arginine for glycine at position 389 in β1 adrenoceptor (Arg389Gly) polymorphism (126, 127). In Europe, heterozygote genotype frequency and homozygote genotype frequency are 40% and 7%, respectively. In the Vanderbil AF Trial conducted by Parvez et al. including 543 patients with AF, the patient group having homozygote Arg389 genotype has been determined to be more resistant to pharmacologic rate control (with various BBs) than the patient group having Gly389 genotype. However, in this trial, only 11% of the patient had HF.

The effect of this genetic polymorphism on rate control in patients with AF has been investigated in the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD) Trial. In this trial, 528 patients with chronic HF (412 in sinus rhythm, 107 with AF) were randomized to bisoprolol and carvedilol groups. The patient group in sinus rhythm had the same response to carvedilol and bisoprolol, independent of genotype. However, patients with AF having homozygote Arg389 genotype have been shown to respond 12 beats less to carvedilol (not bisoprolol) compared to the patient group with at least one Gly389 allele (128).

16.4 What precautions should be taken in risk stratification and warfarin indication?

Atrial fibrillation is a strong risk factor for stroke and thromboembolism (129). It is known that other comorbid conditions (HF, hypertension, age, diabetes, stroke, or history of transient ischemic attack) along with AF increase the risk. $CHADS_2$ and CHA_2DS_2VASc scoring systems are used to stratify the risk in patients as low, moderate and high. Previous trials have demonstated that HF carries a higher risk for thromboembolism compared to other risk factors in these scoring systems (130-133). Therefore, $CHADS_2$ and CHA_2DS_2VASc scores may underestimate the real risk in patients with HF. According to these scoring systems, a patient who has only HF is stratified into moderate-risk group and in such a patient, initiation of anticoagulant therapy remains uncertain. In the high-risk patient group (score ≥2), anticoagulants are definitely recommended; however, in patients who have ≤1 point, decision for antiplatelet or anticoagulant therapy is not clear. In a study conducted by Lee et al. (134) comparing anticoagulants and aspirin, no difference was observed in the rates of major bleeding. In another study, it has been reported that the frequency of cerebrovascular events was lower in the group receiving vitamin K antagonist compared to the group not receiving vitamin K antagonist (135). Considering all these facts, in AF patients with HF, it has been observed that vitamin K antagonists are superior to antiplatelet agents in the moderate-risk group. The ESC AF guidelines recommend OAC use in moderate-risk group whose CHA_2DS_2VASc score is 1; whereas, they do not recommend anticoagulant or antiplatelet use in the low-risk group (score: 0). The ESC recommends antiplatelet use in patients with a CHADS score ≥1 only if the patient refuses anticoagulant therapy.

It makes sense to initiate OAC therapy if the risk of bleeding is not very high in AF patients with HF. The HAS-BLED scoring system (hypertension, hepatic and renal dysfunction, stroke, history of bleeding, labile INR, age (≥65 years), drug and alcohol use) can be used to determine the risk of bleeding (136).

16.5 Should new oral anticoagulant agents be preferred over warfarin?

In patients with HF, vitamin K metabolism is highly variable and this makes it difficult for INR values to remain in the therapeutic range. HF is one of the factors that increase bleeding risk in patients who receive vitamin K antagonists.

The use of new OACs (NOACs) is approved for non-valvular AF. In the RE-LY (Randomized Evaluation of Long Term Anticoagulation Therapy) and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) Trials, it has been shown that dabigatran and apixaban were superior to vitamin K antagonists in terms of reducing adverse clinical outcomes. In the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) Trial, it has been demonstrated that rivaroxaban was not infe-

rior to vitamin K antagonists (137-139). In a recent meta-analysis, new OACs and warfarin were compared in terms of preventing both systemic embolic event and stroke and causing bleeding in AF patients with HF. It has been reported that new OACs reduced systemic embolic event and stroke more than warfarin and that major bleeding and intracranial bleeding occurred less in the NOAC group. Total bleeding rates were similar in NOAC and warfarin groups. This meta-analysis showed that NOACs may be a good alternative for warfarin in patients with HF.

17.0 Drug treatment in hypertension – Timur Selçuk

17.1 What should the blood pressure target be in HF?

In the treatment of hypertension in HF, the type of HF is important. In HF-PEF in which the systolic functions of the heart is normal and diastolic functions are impaired, the blood pressure target should be within the limits recommended by the current hypertension guidelines. Particularly in HF-REF in which systolic functions are impaired, an increase in blood pressure causes an increase in afterload and also causes an increase in preload with an increase in the filling pressures of the heart. This may lead to acute HF manifestation by worsening of the clinical condition of patient. Although target blood pressure has not been stated in current hypertension guidelines for HF, it seems reasonable to keep systolic BP at around 100-120 mm Hg and diastolic BP at around 60-80 mm Hg, which are optimal blood pressures to minimize unfavorable hemodynamic effects generated by high blood pressure. Particularly in the treatment of HF-REF, it should be considered that most of the drugs used by the patients have hypotensive effects and that their hypotensive effects will be potentiated while incrementing the target doses of these drugs and combining them with each other.

17.2 Which antihypertensives can be added to ACEIs/ARBs, Beta-blockers and MRAs?

In patients receiving combination therapy such as with ACEIs/ARBs, BBs and MRAs due to chronic HF-REF, adding diuretics to the combination therapy in order to benefit from their antihypertensive properties is quite favorable in the case of hypertension. Loop diuretics are frequently used in patients with HF in whom fluid overload is significant. Thiazides can be used as the first-line antihypertensive drugs in addition to loop diuretics. In patients with HF-REF, dihydropyridine group of calcium-channel blockers (such as amlodipine, felodipine, nifedipine) with vasodilatation properties and a neutral effect on mortality can be used in the treatment of hypertension accompanied by HF. Isosorbide dinitrate- hydralazine combination is included in the category of drugs that can be effective in mortality in the treatment of HF and it can also be used as an antihypertensive due to its vasodilation properties. Drugs that are effective on the central nervous system (clonidine, moxonidine) and also alpha-adrenergic blockers (prazosin) are not recommended in the treatment of hypertension associated with HF (3). Recommendations for the treatment of hypertension in patients with left ventricular systolic dysfunction and symptomatic HF (NHYA Functional Class II-IV) are given in Table 26 (3).

17.3 Why are Alpha-Blockers and Moxonidine not recommended in hypertension in HF?

Alpha-blockers are agents used in the treatment of hypertension due to their vasodilator properties. The vasodilation properties of alpha-blockers have generated the idea that they can be used in the treatment of HF as well. However, in small-scale pilot trials, it has been observed that risk of HF increased with alpha-blocker therapy. In a double-blind study evaluating the effect of isosorbide dinitrate and ISDN-H combination and prazosin on mortality, ISDN-H combination has been demonstrated to be beneficial on mortality in patients with HF compared to placebo and prazosin has been shown to have no effect on mortality in patients with HF compared to placebo. The ratio of worsening HF was the highest with 8.5% in the prazosin group and it has been found to be 7.5% and 5.5% in ISDN-H and placebo groups, respectively (45). In the ALLHAT Trial, decompensated HF has been observed to be higher in the alpha-blocker group than the diuretic group. Therefore, use of alpha-adrenoceptor antagonists is not recommended in hypertension accompanied by HF because of safety concerns (neurohumoral activation, fluid retention, worsening HF) (140).

Moxonidine is an agent with an inhibition property on central nervous system and is a receptor agonist of imidazole. In the MOXCON Trial where the effect of moxonidine in patients with HF was evaluated, it has been observed to increase mortality and hospitalizations compared to placebo and its use in HF was not recommended by the current guidelines (141).

18.0 Drug treatment in coronary artery disease – Mehdi Zoghi

18.1 Which anti-anginal drugs can be added to beta-blockers?

The ESC Guidelines for HF recommend BB treatment as the first-line therapy in the presence of angina. In patients with contraindication or intolerance to BBs, ivabradine, nitrate, amlodipine, nicorandil or ranolazine can be used instead of BB treatment. In patients in which angina cannot be controlled with BB treatment, one of ivabradine, nitrate, amlodipine, nicorandil or ranolazine can be added to the BB treatment. In systolic HF patients with anginal pain, amlodipine, ivabradine and nitrates can be used safely. The efficacy of nicorandil and ranolazine is controversial in this group of patients. A meta-analysis of 15 randomized clinical trials, where trimetazidine added to the conventional treatment in HF was evaluated, showed that trimetazidine improved NYHA functional class (–0.57, p=0.0003), increased exercise duration (63.75 min., p<0.0001), improved left ventricular EF (6.46%, p<0.0001) and reduced the frequency of hospitalization (RR: 0.43, p=0.03) (3, 142).

Table 26. Recommendations for the treatment of hypertension in patients with HF-REF (3)

Recommendations	Class	Level
Step I		
One or more of an ACEI (or ARB), BB and MRA is recommended as first-, second-, and third-line therapy, respectively	I	A
Step 2		
A thiazide diuretic (or if the patient is treated with a thiazide diuretic, switching to a loop diuretic) is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACEI (or ARB), BB, and MRA	I	C
Step 3		
Amlodipine is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACEI (or ARB), BB, MRA, and diuretic	I	A
Hydralazine is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACEI (or ARB), BB, MRA, and diuretic	I	A
Felodipine should be considered when hypertension persists despite treatment with a combination of as many as possible of an ACEI (or ARB), BB, MRA, and diuretic	IIa	B
Moxonidine is not recommended because of safety concerns (increased mortality). Alpha-adrenoceptor antagonists are not recommended because of safety concerns (neurohumoral activation, fluid retention, worsening HF)	III III	B A

18.2 How effective are nicorandil, ivabradine and ranolazine in angina control?

Although a meta-analysis of 20 trials evaluating the efficacy of nicorandil reported favorable outcomes, most of the trials involved in this meta-analysis were observational, included very heterogeneous HF patient population and the inclusion criteria for each trial varied significantly (3, 143).

Ivabradine is recommended by the ESC HF guidelines as an anti-anginal agent in patients who have CAD with systolic HF in sinus rhythm (3). However, a recently published SIGNIFY trial, in almost 20,000 patients who have CAD with a heart rate >70 b.p.m and without HF, indicated that ivabradine did not reduce cardiovascular death or nonfatal MI, cardiovascular death alone and non-fatal MI alone. Furthermore, SIGNIFY trial pointed out that in patients with angina limiting daily activity, ivabradine may be able to increase cardiovascular death or non-fatal MI (144).

In RALI-DHF (RAnoLazIne for the Treatment of Diastolic Heart Failure) Trial, in HFpEF patients, ranolazine has been shown to provide an improvement in hemodynamic measurements (left ventricular end-diastolic pressure and PCWP) whereas no significant beneficial effect has been found in diastolic echocardiographic or cardiopulmonary exercise parameters. On the other hand, in HFpEF cases with CAD (EF: 58%±10), after 2 months ranolazine use, significant improvements in deceleration time, isovolumetric contraction time and myocardial performance index were reported (145).

These findings suggest that there is no enough data for the efficacy and safety of nicorandil and ranolazine use in angina control in HF. Ivabradine is a drug the efficacy of which has been proven in the treatment of HF-REF. However, more data is required regarding efficacy and safety in patients with CAD and angina.

19.0 Drug treatment in chronic renal disease – Ahmet Temizhan

19.1 Which should be preferred in the management of drug therapy: serum creatinine level or eGFR?

Glomerular filtration rate is usually estimated by serum creatinine concentration. In elderly and very sick patients, since creatinine production will decrease due to a reduction in muscle mass, GFR may be significantly low in these patients even if serum creatinine levels are within normal range or slightly elevated. Therefore, while evaluating the renal functions, estimated GFR adjusted to race, age, weight and gender is recommended to be used instead of serum creatinine. For the correct GFR estimation, the serum creatinine levels should be stable. GFR calculation should not be used in patients whose serum creatinine values increase gradually or are highly variable. Patients with decompensated HF, particularly those receiving intensive diuretic therapy are typical examples in this regard. Therefore, when managing drug therapy in patients with HF, GFR should be used in stable outpatients and creatinine value in decompensated patients receiving diuretics.

19.2 How should drug therapy and monitoring be performed in hyperpotassemia?

Almost all of the drugs that are used in the treatment of chronic HF (RAAS blockers, MRAs, BBs and diuretics) affect serum potassium levels. The risk of hyperpotassemia is very low in patients with normal renal functions; whereas in patients with renal dysfunction, which is frequently accompanied with HF, the risk of hyperpotassemia is higher. However, "patients with renal dysfunction who are very likely to develop hyperpotassemia

Table 27. Initial and maintenance doses of mineralocorticoid receptor antagonists (4)

	eGFR (mL/min/1.73 m^2)			
	≥50		30-40	
	Initial dose (if K ≤5 mEq/L)	Maintenance dose (if K is ≤5 mEq/L at the end of 4 weeks)	Initial dose (if K is ≤5 mEq/L)	Maintenance dose (if K is ≤5 mEq/L at the end of 4 weeks)
Eplerenone	25 mg/day	50 mg/day	25 mg, every other day	25 mg/day
Spironolactone	12.5-25 mg/day	25-50 mg/day	12.5 mg/day or every other day	12.5-25 mg/day

eGFR – estimated glomerular filtration rate

are the patients who will receive the most cardiovascular benefit from the treatment". Therefore, evidence-based HF therapy should be implemented insistently by close monitoring of potassium levels in patients who have HF and renal dysfunction.

Cautions for serum potassium levels in the management of chronic HF should be taken. First of all, it should be ensured that serum potassium measurement is correct and also it should be kept in mind that hypopotassemia is as dangerous as hyperpotassemia. Serum potassium level should be kept above 4 mEq/L. Optimal serum potassium value is between 4–5 mEq/L. However, the values between 5–5.5 mEq/L are considered safe (146). Drugs can be continued as long as serum potassium levels are within the 4.0–5.5 mEq/L range. Close monitoring is mandatory particularly in patients with serum potassium levels between 5 to 5.5 mEq/L, renal dysfunction and/or diabetes (147). If NSAIDs, potassium sparing diuretics and salt equivalents are used, they should be discontinued. Potassium-rich foods should be reduced. The risk of severe hyperpotassemia reduces in patients who are regularly monitored (148, 149). It is not known whether serum potassium levels within a range of 5.5 - 6.5 mEq/L without an ECG change are dangerous or not. However, it is very important to know that severe hyperpotassemia may develop rapidly in these patients (Table 27, Figure 2).

19.3 How should diuretic therapy strategies be arranged in congestion treatment?

There is no absolute diuretic strategy recommended since the dose-response curve of diuretics in patients with congestion varies significantly in each patient and there are no significant differences in the benefit-risk ratio among parenteral routes of administration (3, 4). Individual administration of furosemide and thiazide group of diuretics, the most commonly used diuretics in in-patients and outpatients under monitorization, is as follows:

In-patients: Whether the patient used diuretic previously and the patient's response to the drug should be evaluated. If the patient is diuretic-naïve, i.v. low dose (≤1 mg/kg daily) furosemide should be initiated and the dose should be adjusted according to the response. If the patient had previous diuretic use, i.v. administration of the previous oral dose of furosemide (represents low dose for these kinds of patients), or in case of severe congestion, i.v. administration of 2.5 times the oral dose are recemmended (represents high dose) and then the dose should be adjested according to the response (see Table 28 which helps up-titration of the dose).

Table 28. Recommendation for furosemide dose up-titration in patients under diuretic therapy* (151)

Previous dose	Recommended dose
≤80 mg	40 mg i.v. bolus + 5 mg infusion/hour
81-160 mg	80 mg i.v. bolus + 10 mg infusion/hour
161-240 mg	80 mg i.v. bolus + 20 mg infusion/hour
>240 mg	80 mg i.v. bolus + 30 mg infusion/hour

*Adapted from CARRESS HF study (150)

Table 29. Monitorization of patients receiving diuretics at hospital

1- Daily weight monitorization is safer and easier than monitoring fluid output
2- Urinary catheter should not be routinely placed because of infection risk
3- Daily fluid intake should be monitored (See fluid restriction part)
4- Daily blood pressure monitorization should be performed
5- Monitorization of renal functions and electrolytes should be arranged according to the patient; • Frequency of monitorization can be decided according to the eGFR value at the time of initiation of therapy. It will be enough to measure renal functions every day if eGFR value is <30 and every 3 days if ≥30 • GFR is not reliable in patients receiving intensive diuretic therapy as creatinine values will show a dynamic change. Therefore, it is more appropriate to monitor renal functions according to creatinine levels

Intravenous administration can be performed as 24-hour infusion or bolus injection in doses divided into two. The maximum daily dose is 600 mg (3, 4). Other loop diuretics can be used in accordance with doses equivalent to 40 mg of furosemide (torasemide 20 mg and bumetanide 1 mg) (3, 4). Thiazide group diuretics can be added to the treatment in patients with eGFR ≥30 mL/min/1.73 m^2 (3, 4). Metolazone is approximately a 10 times more potent thiazide diuretic than hydrochlorothiazide (HCTZ) (3, 4). It can replace HCTZ in resistant patients. Generally, once daily dose is enough. The monitorization of the patient should be close and individual (Table 29).

Evaluation of the diuretic response and dose adjustment: Almost 500 gr to 1 kg daily weight loss is expected. I.V. loop diuretic is continued until congestion signs disappear (mostly equivalent to dry weight). After dry-weight is ensured, the initial high-dose is decreased to the dose that can maintain dry-weight according to renal functions. It should be switched to oral dose when congestion disappeared. Double dose of the last parenteral dose is administered orally. The dose is divided into two and must be taken before meals. Parenteral diuretics can be given as long as systolic blood pressure is ≥90 mm Hg. Serum potassium levels should be kept at ≥4 -5.5 mEqL. If serum sodium value is <125 mEq/L despite high-dose treatment, tolvaptan should be added.

Outpatients: Whether the patient used diuretic previously and the patient's response to the drug should be evaluated. If the patient is diuretic-naïve, 40 mg/day furosemide is initiated. The dose is divided into two and should be given before meals. If the patient had previous diuretic use, a double dose of the previous furosemide dose is given. The dose is divided into two and should be given before meals. Oral furosemide dose adjustment is performed according to weight loss, renal functions and electrolyte levels.Frequency of monitorization can be decided according to the eGFR value at the time of initiation of therapy. It will be enough to measure renal functions after 3 days if eGFR value is <30 ml/min and after one week if ≥ 30 ml/min. However, it is more appropriate to monitor renal functions according to creatinine levels.Almost 500 gr to 1 kg daily weight loss is expected. The dose should be up-titrated step by step until desirable weight loss is ensured and congestion signs disappear. HCTZ may be added to the treatment along with furosemide dose titration. There is no commercially available single HCTZ preparation in our country. Therefore, combinations with RAAS blockers or spironolactone can be considered. In patients without high blood pressure, uptitration to 25 and 50 mg of HCTZ doses with spironolactone combination can be preferred for diuretic efficacy and to avoid hypotension. Serum potassium levels should be kept at ≥4 -5.5 mEqL. Daily maximum dose should be 600 mg for furosemide and 50 mg for HCTZ in compliant patients to the treatment (3, 4); if congestion does not improve or renal functions are impaired despite these doses, the patient should be hospitalized.

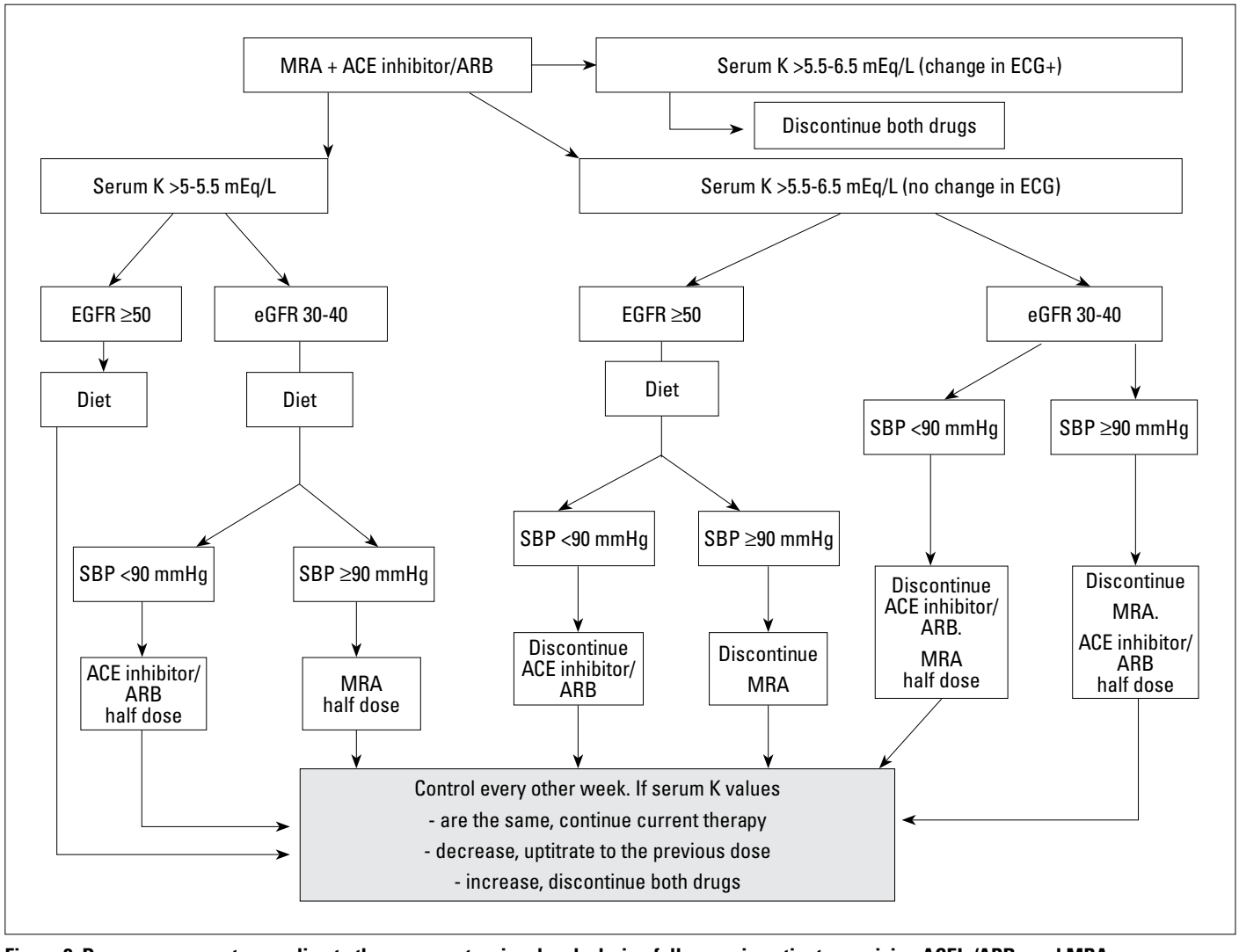


Figure 2. Drug management according to the serum potassium levels during follow-up in patients receiving ACEIs/ARBs and MRAs

General precautions: Weight monitorization (see Weight Monitorization part), blood pressure monitorization and monitorization of daily salt consumption including salt equivalents should be implemented. Adherence to drug therapy and discontinuation of NSAIDs should be ensured.

19.4 Can tolvaptan be an alternative to diuretics in congestion?

Tolvaptan is an active vasopressin antagonist that can be used orally. With its aquaretic effect, it has an important place in the treatment of HF in increasing serum sodium levels in euvolemic and particularly in hypervolemic patients with hyponatremia. In HF patients with persisting hyponatremia (<125 mEq/L) despite the use of high-dose diuretic therapy, tolvaptan is an appropriate treatment approach, regardless of presence of congestion. However it should be kept in mind that It is not alternative, but an adjuvant approach to diuretic therapy and can shorten the duration of hospital stay.

Tolvaptan is initiated with 15 mg daily. Caution is required on the increase in serum sodium level that should not be exceeded >1.0 mmol/L/hour in the first 8 hours (risk of osmotic demyelination syndrome). After a 2-days treatment, it can be increased to 30 mg if enough diuretic efficacy and/or increase in serum sodium levels are not ensured.

Although there is not enough published data regarding its safe and effective long-term use (>30 days) (151, 152), if hyponatremia persists when the drug is discontinued, it can be administered for a longer period of time. However, if serum sodium level is under control with other diuretics after hyponatremia is corrected, long-term use of tolvaptan is not necessary.

19.5 Does torasemide provide any advantage over furosemide?

Although open-label, observational Torasemide in Chronic Heart Failure (TORIC) Trial has not been designed for mortality, total and cardiovascular mortality have been found to be lower in patients treated with torasemide than the patients receiving furosemide (and other diuretics) (153). Further improvement in functional capacity and less abnormality in serum potassium levels in patients receiving torasemide are considered related to the drug's high bioavailability (154) and anti-aldosteronergic effect (155).

If we consider that furosemide as the most commonly used diuretic in patients with HF does not provide same level of efficacy in each patient, we can say that torasemide present an advantage over furosemide. Oral initial dose of torasemide is 10-20 mg o.d. and can be increased up to 200 mg.

19.6 How can we realize whether the worsening renal functions are related to RAAS blockers or renal failure?

In patients with HF in whom serum creatinine levels are elevated and/or GFR reduced, it is important to differentiate cardiorenal syndrome and drug-related changes from each other. However, it is not always possible to differentiate. In some patients all can co-exist (156). Marked proteinuria (generally >1000 mg), urinary sediment changes concurrent with hematuria, small size of kidneys in radiological evaluation should suggest underlying renal disease. Normal urinalysis is typical in cardiorenal syndrome and drug-dependent changes; however, it should be kept in mind that in case of nephrosclerosis and obstructive nephropathy, urinalysis is normal as well.

There may be a 30% elevation in serum creatinine levels with RAAS blockers. This elevation is mostly a reflection of angiotensin II inhibition rather than impairment in renal dysfunction (157, 158). However, RAAS blockers can also be nephrotoxic so as to cause severe impairment in renal functions. Drug-related changes in renal functions are observed 3-5 days after the drug is initiated and become stable in 7 days unless it is nephrotoxicity (159). If the patient's serum creatinine value increases by ≥50% or 1.5 times of basal value in 48 hours and urine output decreases (urine output <0.5 mL/kg/hour for longer than 6 hours)

Table 30. KDIGO classification for acute kidney injury (160)

Stage	Serum creatinine	Urine output (UO)*
1	An increase of 1.5-1.9 times the basal value or 0.3 ≥ mg/dL increase	UO <0.5 mL/kg/hour (for 6-12 hours)
2	An increase of 2.0-2.9 times the basal value	UO <0.5 mL/kg/hour (for ≥12 hours)
3	An increase of 3.0 times the basal value or creatinine being ≥ 4.0 mg/dL or dialysis requirement or eGFR being <35 mL/min/1.72 m^2 in patients <18 years of age	UO <0.3 mL/kg/hour (for ≥24 hours) or anuria for ≥12 hours

*Reduction in urine output is a fairly sensitive marker of renal dysfunction. It occurs usually before an elevation in creatinine. It should be kept in mind that urine output can be affected by diuretic use

dependent on the drugs, it can be concluded that acute kidney injury is about to start (Table 30). If renal dysfunction persists and gradually progresses in patients with chronic HF receiving RAAS blockers, patients should be closely monitored and investigated (Figure 3). Information on renal functions of the patient before treatment or in stable periods helps making a differential diagnosis of renal dysfunction that develops later (Table 31). Therefore, the most important examination to be performed in routine follow-up of patients with chronic HF is renal functions.

19.7 How can we optimize drug therapy in pre-dialysis and dialysis patients?

Since patients with chronic renal disease are not included in most of the major HF trials, there is not enough evidence regarding the use of RAAS blockers and their possible clinical outcomes in pre-dialysis patients and patients who undergo regular dialysis program. HF treatment guidelines recommend that RAAS blockers should be cautiously used in the presence of chronic renal disease (CRD) and although there is not a clear contraindication, they restrict the use of these drugs in patients with eGFR value <30 mL/min/1.73 m^2 (3, 4). In fact, it makes sense to be expected that RAAS blockers, which are the cornerstones of treatment in HF, affect prognosis favorably in patients who have HF in association with CRD. Based on the results of retrospective studies (163, 164), expert opinions (165) and KDIGO recommendations (166), it has been pointed out that these patients may benefit from RAAS blockers with appropriate follow-up. In a recent prospective cohort analysis, it has been reported that in HF patients with severe renal disease (creatinine clearance <30 mL/min, Stage 4-5 CRD), RAAS blockers reduced all-cause mortality (167). We are look-

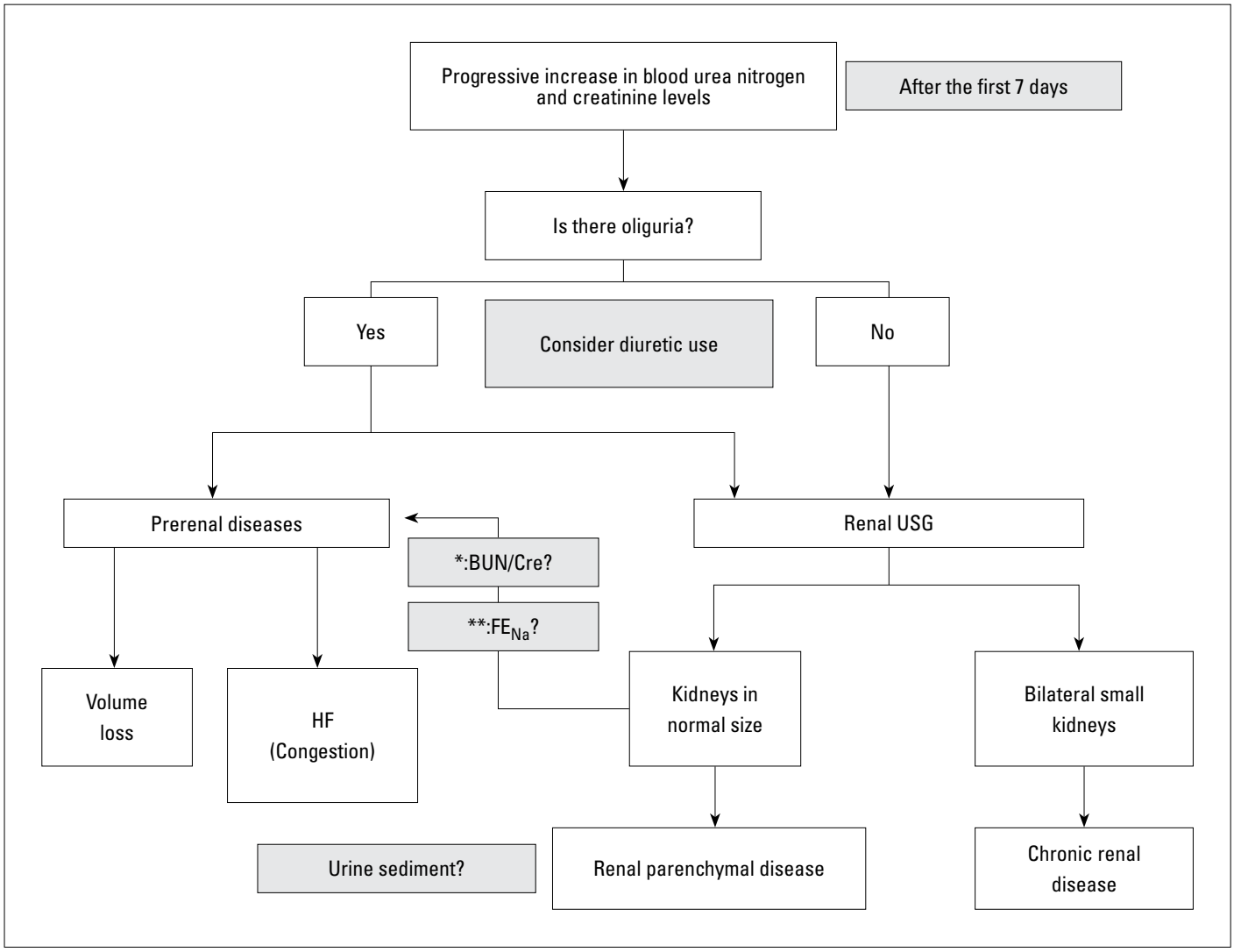


Figure 3. Approach to patients with chronic HF whose renal functions impair in the course of the therapy (162, 163)

*Blood urea nitrogen/creatinine ratio (BUN/Cre) is commonly used to differentiate pre-renal failure from the underlying renal disease. Increased BUN/Cre ratio (if there is no increase in urea production) typically indicates pre-renal etiology; **FE_{Na}: fractional excretion of sodium (162)

FE_{Na} = 100 x (urine sodium x serum creatinine)/(serum sodium x urine creatinine)

If FE_{Na} is <1%, pre-renal possibility is high (can be acute glomerulonephritis, contrast nephropathy, rhabdomyolysis, urinary obstruction)

If FE_{Na} is >2% it is very likely to be kidney-related

Table 31. Possible AKI, ARD and CRD diagnoses (160) according to GFR and serum creatinine

Patients with basal GFR value ≥60 mL/min/1.73 m²		
Increase in serum creatinine (for 7 days)	GFR (for 3 months)	Diagnosis
>1.5 folds	Unchanged	AKI
<1.5 folds	<60	ARD (no AKI)
<1.5 folds	>60	No known renal disease
Patients with basal GFR value <60 mL/min/1.73 m²		
Increase in serum creatinine (for 7 days)	GFR (for 3 months)	Diagnosis
>1.5 folds	Unchanged	AKI+CRD
<1.5 folds	>35% reduction	ARD (no AKI) +CRD
<1.5 folds	<35% reduction	CRD

AKI – acute kidney injury; ARD – acute renal disease; CRD – chronic renal disease; GFR – glomerular filtration rate

ing forward to hearing about the results of trials conducted with drugs such as RAAS blockers (for example, selective non-steroidal aldosterone blockers) and better-tolerated potassium binding polymers that are currently under investigation. In the light of this information, basic drug recommendations in dialysis and predialysis patients with HF are summarized in Table 32 and Table 33.

When interpreting the recommendations concerning the use of drugs, the followings should be considered: These basic drugs are beneficial in HF patients with CRD. We should try to use them as much as possible. It is appropriate neither to use them in every patient nor to restrict with the side effect concerns. Therefore, considering the evidence and general aspects (Table 33), prioritizing safety when using RAAS blockers and individualizing the treatment are the most accurate approaches in this patient group in whom cardiovascular mortality is high.

20.0 Drug treatment in diabetes mellitus – İbrahim Sarı

20.1 Which antidiabetics should be used? Which should be avoided?

Metformin is the first choice drug as monotherapy or in combination in the treatment of diabetes (Table 34). It reduces hepatic glycogenesis, increases insulin sensitivity, peripheral glucose uptake, and reduces glucose absorption from the intestine. Since metformin was believed to increase the risk of lactic acidosis, it has been considered as contraindicated in HF for a long time. However, it was demonstrated that this risk was actually much lower and not more than other anti-diabetics. Furthermore, when used alone or in combination with sulphonylureas in HF, metformin reduced mortality compared to sulphonylureas alone in observational studies. Therefore, in 2007 FDA removed the warning that metformin was contraindicated in HF. To summarize, regardless of the presence or absence of HF metformin is the first-line treatment in all diabetics unless there is a contraindication.

Sulphonylureas increase insulin secretion from pancreatic beta-cells. There is no prospective study regarding its use in HF. Observational studies show that sulphonylureas are not associated with worse outcome in patients with HF. End-points with metformin are better in studies comparing sulphonylureas with metformin in patients with HF. Due to its risk of hypoglycemia and weight gain, it is recommended that patients with HF should be careful about these effects of sulphonylureas. In summary, it seems rational that they should be used in addition to metformin or in whom metformin is contraindicated, rather than as a first-line therapy (Table 34).

Table 32. Basic drug recommendations in HF patients with CRD

Drug	Stage 3 CRD (eGFR 30–59 mL/min/1.73 m²)	Stage 4–5 CRD (eGFR <30 mL/min/1.73 m²)
ACEIs	Recommended in all HF patients with LVEF ≤40% (31, 169, 170).	They can be used, however renal functions and electrolytes should be closely monitored (31, 169, 170).
ARBs	Recommended in all HF patients with LVEF ≤40%; if there is ACEI intolerance or if symptoms persist despite ACEI and BB therapy but there is MRA intolerance (171, 172).	They can be used, however renal functions and electrolytes should be closely monitored (173).
MRAs	Recommended in all HF patients with LVEF ≤35%; if symptoms persist despite ACEI and BB therapy (15, 16, 174).	Not recommended - no evidence
BBs	Recommended in all HF patients with LVEF ≤40% (31, 170, 171) (175-178)	Recommended in all HF patients with LVEF ≤40% (175-179)

CRD – chronic renal disease; eGFR – estimated glomerular filtration rate; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; MRA – mineralocorticoid receptor antagonist; BB – beta-blocker; EF – ejection fraction

Table 33. General matters that should be known in patients receiving RAAS blockers

– Primarily, we should try to administer ACEI (ARB) and MRA combination. If the patient cannot tolerate (hyperkalemia, hypotension, progression in renal dysfunction) and we have to give only one RAAS blocker, ACEIs (ARB) should be preferred (180) • In clinical trials, MRA was used as an add-on therapy to ACEI (ARB). The results are not known if MRA is given alone • We have evidence that ACEIs (ARB) are beneficial without MRAs
– High-dose RAAS blockers reduce cardiovascular end-points more than their low doses. However, considering that renal dysfunction, hyperkalemia and hypotension are less in low doses, we can say that although the benefit reduces, even low doses are better than not taking them at all • In the subgroup analyses of randomized trials, in HF patients with reduced GFR, it has been determined that relative risk reduction with ACEI/ARB, BB and MRA therapy is similar in patients with normal renal functions (even more absolute risk reduction) (166)
– Benefit-risk balance should be carefully assessed when initiating RAAS blockers in Stage 4-5 CRD (eGFR value <30 mL/min/1.73 m^2), although they affect prognosis favorably
– Close monitorization of renal functions and serum potassium level is essential after initiating the drugs. Although there is no standard monitorization method, methods used in randomized clinical trials can be used • For example, in EMPHASIS-HF Trial, dose was reduced if serum potassium level was 5.5-5.9 mmol/L, discontinued if ≥6.0 mmol/L. The drug was restarted when the potassium level returned to ≤5.0 mmol/L after 72 hours (16) • In the dose adjustment of RAAS blockers, blood pressure should be considered as well as basal renal functions and individual approach should be implemented (See How should treatment be arranged and monitorization be performed in hyperpotassemia?)
ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; BB – beta-blocker; CRD – chronic renal disease; eGFR – estimated glomerular filtration rate; RAAS – renin angiotensin aldosterone system; MRA – mineralocorticoid receptor antagonist

Glitazones (Thiazolidinediones) improve the presentation and function of glucose transporters in adipose tissue, muscle and heart by increasing insulin sensitivity. They decrease unesterified fatty acid use by myocardium. While they have favorable effects on lipid profile, they can worsen HF due to fluid retention. This worsening is more marked in concurrent insulin users. FDA emphasizes that glitazones are contraindicated in patients with NYHA functional capacity III-IV and that they should be used with caution in NYHA functional capacity I-II patients. The ESC HF guideline state that glitazones should not be used in HF patients.

Insulin: Most of the patients require insulin as monotherapy or in combination. Although there are no trials investigating the effect of insulin primarily in HF patients, it appears to be safe. It has (+) inotropic effect on myocardial tissue and improves hemodynamics in HF. However, sodium retention and weight gain are among its adverse effects. The end-points of studies regarding insulin use in HF are controversial. If it is used, patients should be monitored regularly, particularly regarding hypoglycemia and fluid retention (Table 34).

Incretin Secretion Modulators contain a group of gastrointestinal proteins regulating the glucose metabolism with more than one mechanism. They contain glucagon-like peptide agonists (GLP-1) (exenatide, albiglutide, lixisenatide, and liraglutide) and dipeptidyl peptidase–4 inhibitors (DPP-4) (sitagliptin, saxagliptin, vildagliptin, alogliptin, and linagliptin). Since they are activated by food, they are particularly effective in the treatment of postprandial hyperglycemia. They appear to be attractive alternatives since hypoglycemia and other side effects are observed less. Preclinical and small scale studies have shown that they have favorable effects on cardiac hemodynamics. There are controversial publications that sitagliptin and saxagliptin increase HF hospitalizations. Ongoing major trials will provide clearer information regarding the efficacy and safety of this group of drugs in patients with HF.

Table 34. Recommendation on the use of antidiabetic agents in heart failure

Drug/Group	Use/Comment
Metformin	First choice Contraindications: eGFR <30 mL/min, shock, sepsis
Sulphonylureas (Glipizide, Gliclazide, Glibenclamide, (Glyburide), Glimepiride, Gliquidone) Sulphonylurea-like Group, Glinides (Repaglinide, Nateglinide)	Can be used in addition to metformin or in patients in whom metformin is contraindicated. Caution for hypoglycemia and weight gain
Glitazones (pioglitazone, rosiglitazone)	Contraindicated in HF because of fluid retention risk
Insulin	End-point data is controversial. It may cause sodium retention and weight gain
Incretin Secretion Modulators	They mostly prevent postprandial hyperglycemia, risk of hypoglycemia is low, data concerning their efficacy and safety in patients with HF is controversial, major trials are ongoing

20.2 Does diabetes affect choice of beta-blocker?

Historically, BBs were avoided in diabetic patients. The main reasons for this are their potential to suppress the response of the body to hypoglycemia (palpitation and tremor) and the consideration that recovery from hypoglycemic status is longer in patients on BBs (the suppression of glucose production in the liver due to beta2 receptor blockade). However, most clinical studies have shown that this unfavorable effect is no more than a placebo.

Currently, BBs are one of the key molecules in the treatment of HF. A meta-analysis including major trials conducted with BBs (1883 diabetic and 7042 non-diabetic patients) has shown that survival advantage provided by BBs were present in both diabetic and non-diabetic group (relative risk 0.77 in diabetics, 0.65 in non-diabetics). There was no statistically significant difference regarding the risk reduction between diabetic and non-diabetic patients (180).

Therefore, the recommendations of both ESC and ACCF/AHA guidelines concerning BBs are similar for diabetic and non-diabetic patients. Moreover, it is emphasized that the ratio of BB use is lower in diabetic patients. In clinical practice, almost one third of HF patients are diabetic. There is no recommendation in guidelines regarding BB selection in HF patients with diabetes.

In the GEMINI Trial including diabetic hypertensive patients, while metoprolol tartrate worsened insulin resistance, carvedilol had a neutral effect (181). Carvedilol was also superior in terms of the effects on lipid profile. In the COMET Trial, the ratio of new-onset diabetes was 22% less in the carvedilol group when compared with the metoprolol group (p=0.039) (182).

In conclusion, although there are no end-point trials comparing the BBs with each other in HF patients with diabetes, it can be suggested that carvedilol has more favorable metabolic effects than metoprolol, but we cannot make any comparison with bisoprolol and nebivolol.

20.3 Does diabetes affect choice of diuretic?

The effect of diuretics on mortality is not known in HF; whereas they reduce edema and improve shortness of breath. Therefore, in patients with signs and symptoms of congestion, they are recommended by the guidelines regardless of EF.

Diuretics should be used in the lowest possible dose to obtain the dry weight of the patient. The reason for this is the potential adverse effects, such as hypotension, worsening renal function, electrolyte imbalance, hyperuricemia and overactivation of the sympathetic and renin angiotensin aldosterone systems. Other than these, diuretics have unfavorable effects on the glucose metabolism. They may trigger hyperglycemia and cause insulin resistance. Their unfavorable effects on glucose levels are dose-related, and the dose relationship is more significant with thiazide diuretics. Since there is a predisposition to the above mentioned impairments in diabetic patients, keeping the diuretic dose as low as possible is even more important in these patients.

There is not enough data to evaluate whether the effects of diuretics are the same in diabetic or non-diabetic patients with HF. However, it may be considered that the general criteria concerning diuretic use in diabetic patients are the same as in non-diabetics (183).

20.4 What are the important points in insulin use?

Insulin is necessary in the majority of diabetic patients either as monotherapy or in combination. Insulin has a (+) inotropic effect on myocardial tissue and improves hemodynamics in HF. Although there is no major trial investigating the effect of insulin primarily in HF patients, it appears to be safe. However, sodium retention and weight gain are among its adverse effects. Since insulin-dependent fluid retention is central rather than a peripheral edema (pretibial edema), it can be overlooked. In order to deal with this condition, patients can be educated about salt restriction, and/or the diuretic dose can be increased. Another important side effect of insulin is hypoglycemia. Patients with HF should be more careful about hypoglycemia because majority of the patients are using BBs.

The end-points of studies regarding insulin use in HF are controversial. In the CHARM trial, primary end-point was worse in diabetic patients using insulin than the patients not using insulin (184). It can be suggested that worse outcome in the group receiving insulin was related to longer period of diabetes and more advanced stage of the disease in the group using insulin.

To summarize, a substantial number of patients need insulin; however, if it is used patients should be monitored regularly with particular attention to hypoglycemia and fluid retention.

21.0 Drug treatment in chronic obstructive pulmonary disease (COPD) – İbrahim Sarı

21.1 Which beta-blocker to choose and at what dose in COPD?

The concern that BBs may trigger bronchospasm in patients with HF accompanied by chronic obstructive pulmonary disease (COPD) causes the use of BBs to a lesser extent than necessary in this group of patients. Investigations reveal that the most important reason for not using BBs or using them less than necessary in patients with HF is the presence of COPD. However, according to current data and guideline information, the presence of COPD does not constitute a contraindication for BB use alone (185).

With the exception of advanced stage COPD, beta-1 selective agents (bisoprolol, metoprolol succinate, nebivolol) can be safely used in COPD. In a study including 35 patients with concurrent HF and COPD (186), the effects of BBs on lung functions were investigated. The FEV1 value (forced expiratory volume in 1 second) was lowest with carvedilol and highest with bisoprolol (carvedilol 1.85 [95% CI, 1.67-2.03]; metoprolol 1.94 [95% CI, 1.73-2.14]; bisoprolol 2.0 [95% CI, 1.79-2.22]).

The most important matter in the use of BBs is that the starting dose should be kept lower and dose incrementing be done more gradually than patients without COPD. It is better to be cautious about the use of carvedilol, a non-selective BB, in patients with COPD since it has a higher risk of causing bronchospasm and can prevent the bronchodilator response to beta-2 agonists (187).

21.2 ACE inhibitor or ARB use in case of frequent cough in patients with COPD?

The guidelines emphasize that ACEIs should be used in all patients with HF-REF unless there is a contraindication and ARBs in patients who cannot tolerate ACEIs.

The prevalence of COPD is approximately 20-30% in patients with chronic HF. The additional potential benefits of ACEIs in HF patients with accompanying COPD can be explained as follows: Angiotensin II is a potent constrictor for airways. ACEIs relieve the obstruction in the airways by lowering the level of angiotensin II. They reduce pulmonary inflammation and pulmonary vascular constriction. They have favorable effects on gas exchange from alveolar membrane.

However, because by ACEIs might cause cough it can be confusing in patients with accompanying COPD. The following should be considered in cough complaints of HF patients with accompanying COPD who receive ACEIs: (1) Cough is one of the main symptoms of COPD. Therefore, it may be related to the nature of COPD, worsening of COPD or concurrent lung infection. It is important to know that in general COPD-related cough contains secretion and is productive. In this case, COPD treatment should be re-evaluated. There is no need to switch from ACEIs to ARBs. (2) Cough may be related to worsening of HF i.e. increased pulmonary congestion. The cause may be found by history, physical examination and laboratory examinations (such as NT-proBNP). Initially the cough may be dry but by time it might become productive. In this case, the HF treatment should be intensified (such as increasing the diuretic dose). There is no need to switch from ACEIs to ARBs. (3) In patients receiving ACEIs, a dry persistent cough may occur. Although its mechanism is not known completely, it is considered to be related to bradykinin accumulation resulting from slowing of the bradykinin degradation by ACEIs. Incidence of ACE inhibitor related cough varies from 0.5% to 25% and is higher in women. If the patient's cough is considered to be associated with ACEIs, they should be changed with one of the guidelines-recommended ARBs (valsartan, candesartan or losartan).

The only way to understand whether the cough is associated with ACEI is to monitor the course of cough after discontinuation of the drug. In clinical practice, it may not always be easy to differentiate which one of the abovementioned three conditions is associated with cough. In this case, the course of the cough can be monitored by switching from ACEIs to ARBs.

21.3 Which inhaled bronchodilators should be chosen in HF accompanied by COPD?

COPD is a disease characterized by progressive airflow restriction which is not entirely reversible. Inhaled bronchodilators constitute the basis of treatment in symptomatic COPD patients. Inhaled bronchodilators are basically comprised of beta-2 agonists and anticholinergics.

Beta-2 Agonists are divided into two groups as short-acting (salbutamol [Ventolin] and terbutaline) and long-acting beta-2 agonists (salmeterol [Serevent] and formoterol [Foradil, Ventafor]). Beta-2 agonists cause bronchial smooth muscle relaxation by stimulating intracellular cAMP. Beta-2 agonists improve lung functions, reduce symptoms, increase exercise capacity, reduce exacerbations and improve quality of life in COPD. However, beta-2 agonists cause an increase in myocardial oxygen consumption by increasing the heart rate. They might cause hyperglycemia, hypokalemia, hypomagnesemia and QT prolongation. These adverse effects are more marked particularly with short-acting beta-2 agonists and cause more problems in patients with accompanying HF. Beta-2 receptors are preserved in number and function whereas there is reduced beta-1 receptor number and activity in HF. Therefore, risk of adverse effects increase in patients with HF associated with the excessive cardiovascular sympathetic response to short-acting beta-2 agonists (185). The abovementioned adverse effects are observed much less with long-acting beta-2 agonists and long-acting beta-2 agonists are safer in patients with HF. Consequently, if a beta-2 agonist will be used in concurrent COPD and HF, long-acting beta-2 agonists should be preferred (186).

Anticholinergics are divided into two groups as short-acting (ipratropium bromide) and long-acting anticholinergics (tiotropium [Spriva] and aclidinium). Anticholinergics ensure bronchodilation by blocking muscarinic receptors. Inhaled anticholinergics are at least as effective as beta-2 agonists and safer than beta-2 agonists in terms of cardiovascular adverse effect profile. Therefore, they are the primarily preferred inhaled bronchodilators in concurrent COPD and HF (187).

There is not enough data regarding whether to use long-acting beta-2 agonists or anticholinergics as first choice in concurrent COPD and HF. There are concerns about possible interaction of beta-2 agonists with BBs used in HF, and it is known that the cardiovascular adverse effects of anticholinergics are less than beta-2 agonists. Within this context, it can be suggested that, at least theoretically, anticholinergics may be preferred over beta-2 agonists. However, it should be kept in mind that most of the patients require combination of these two agents.

21.4 What to do when corticosteroid is required in COPD?

Corticosteroids are the main elements of pharmacological therapy in patients with COPD. Corticosteroids are frequently used both during and in preventing attacks in COPD. Corticosteroids can be used through IV or oral route or as an inhaler, depending on the stage and presentation of the disease. Cortico-

steroids should be used cautiously in patients with accompanying HF. Since steroids cause fluid and salt retention, they may cause congestion in HF patients. They should therefore be used for the shortest time possible. When used, inhaled forms should be preferred, if possible, to minimize systemic side effects.

22.0 Treatment in pulmonary hypertension associated with left heart failure (Group-2 PH) – Mehmet Serdar Küçükoğlu

22.1 Can PAH-specific treatment be used in severe PH associated with left heart disease?

Pulmonary hypertension (PH) associated with left heart disease (PH-LHD) is considered Group II PH (188) (Table 35). For years, valve diseases, particularly mitral stenosis, have been the frequent cause of PH-LHD (189). PH is detected in 15% of patients with mitral regurgitation during rest and in 46% during exercise (190). PH incidence in aortic stenosis has been reported as 30% (191).

Recently, Heart Failure with Preserved Ejection Fraction (HF-PEF) has been the most frequently reported PH-LHD cause. In patients with HF-PEF, PH frequency and clinical properties have been investigated with observational studies (192). It has been reported that PH was observed more in patients with HF-PEF who have comorbidities such as advanced age, obesity, DM, COPD, hypertension, CAD and atrial arrhythmias.

In Heart Failure with Reduced Ejection Fraction (HF-REF), PH frequency varies depending on the severity of disease, PH definition used and group of patients investigated in HF-REF (193).

In PH-LHD, the treatment is intended to treat the underlying disease. PH regresses with surgical correction of valves and optimization of HF treatment. In both precapillary and postcapillary PH patients with increased pulmonary vascular resistance, which cannot be corrected with medical and/or surgical methods, no significant benefit was observed in the trials conducted to investigate whether PAH-specific drugs might be beneficial (Table 36). The RELAX Trial conducted with sildenafil which was the most promising agent among current PAH-specific treatments resulted in disappointment (193). In the light of current data, the ESC Guidelines do not recommend the use of PAH-specific treatment in PH associated with left heart (Class III indication).

Table 35. Current PH Clinical Classification. 2015 ESC/ERS Pulmonary Hypertension Guidelines (188)

Group 1	Pulmonary Arterial Hypertension (PAH)
Group 2	Pulmonary Hypertension Associated with Left Heart Disease
Group 3	Pulmonary Hypertension Associated with Lung Diseases and/or Hypoxia
Group 4	Chronic Thromboembolic Pulmonary Hypertension
Group 5	Pulmonary Hypertension with Unknown and/or Multifactorial Mechanism

22.2 Is high-dose nitrate beneficial in the presence of severe PH due to left heart disease?

The physiopathology of PH comprises pulmonary vasoconstriction, intimal and smooth muscle proliferation, in situ thrombosis and, pathological remodeling processes of pulmonary arteries. Although PH formation is accepted as being multifactorial, it starts with impairments in vasodilator (NO and prostaglandin pathways) and vasoconstrictor (endothelin-1, angiotensin II)

Table 36. Trials conducted with PAH-specific treatments in HF

Drug	Study acronym	Patient population	PH as inclusion criteria	Outcome
Epoprostenol	FIRST	HF low EF NYHA III-IV (n=471; 2y)	No	Trial terminated early because of strong trend toward increased mortality
Bosentan	ENABLE	HF low EF NYHA III-IV (n- 1613; 1.5 y)	No	No improvement in clinical status; increased risk of fluid retention
Bosentan	Kaluski	HF low EF NYHA III-IV (m = 94; 20 wk)	Yes	No difference in hemodynamic or echocardiographic parameters; more serious adverse events
Darusentan	EARTH	NYHA II-IV (n=642)	No	No change in cardiac remodeling or outcome
Tezosentan	RITZ-5	Acute pulmonary edema	No	No change in oxygen saturation; Outcome worse with higher dose
Sildenafil	Observational study	HF, 6 mo (n=40)	No	Improved heart rate recovery with sildenafil
Sildenafil	Randomized study	HF low EF, NYHA II -IV (n=34)	Yes	Reduction in PAP, peak VO_2, 6-min walk distance and fewer hospitalizations
Sildenafil	Observational study	HF, 6 mo (n=46)	No	Reduction in PAP, peak VO_2, and ventilatory efficiency

pathways. On the basis of this information, drugs affecting the NO pathway (phosphodiesterase 5 inhibitors, guanylate cyclase stimulants), prostanoids and endothelin receptor antagonists have been accepted as PAH-specific treatments.

Although nitrates are used with hydralazine in special groups of patients in chronic HF and intravenously in acute decompensated HF, there is very limited information about their use in patients who have developed PH. Systemic hypotension limits their use in this group of patients. Concurrent oral nitrate use with sildenafil in 3 patients in one publication has given favorable results (194). Their use reduced vascular resistance and pulmonary pressure and did not cause systemic hypotension. However, it should be kept in mind that sildenafil and nitrate combination is contraindicated due to severe systemic hypotension risk.

22.3 Can sildenafil be used in the case of severe PH associated with left heart disease?

In a meta-analysis combining trials conducted in the recent years, it has been reported that sildenafil improved pulmonary hemodynamics especially in the HF-REF group and did not show the feared side effects (195). This meta-analysis included 6 HF-PEF trials and 3 HF-REF trials. Evidence showed that oxygen consumption and EF increased significantly in the HF-REF group and no clinical worsening was observed. New trials are required in the HF-REF group since there is no result concerning mortality in this meta-analysis.

Basic treatment in HF-PEF is intended to improve left ventricular diastolic functions and to reduce pulmonary venous pressure. However, although we have evidence that pulmonary vascular disease may be the primary treatment target, this evidence is very limited. Endothelin receptor antagonists and prostanoid trials have given either neutral or unfavorable results (196). In two ongoing trials, ambrisentan (The Safety and Efficacy Trials to Treat Diastolic Heart Failure Using Ambrisentan) and bosentan (The Safety and Efficacy of Bosentan in Patients with Diastolic Heart Failure and Secondary Pulmonary Hypertension (BADDHY)) are being investigated in the HF-PEF group.

Recently, much evidence has been published concerning the fact that prevention of cyclic GMP degradation with PDE-5 inhibition may be beneficial by targeting the right ventricle (RV) and pulmonary vessels in patients with PH associated with left heart disease (196). This benefit is due to PDE-5 inhibition found in large amounts in pulmonary arteries and intrapulmonary circulation. Thus, systemic vasodilation is less.

Despite favorable studies, use of sildenafil 60 mg t.i.d has not shown any benefit in the RELAX (Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People With Diastolic Heart Failure) Trial. However, pulmonary hemodynamics and right ventricular functions have not been evaluated in this trial (196). Well-planned mortality and morbidity trials are required to elucidate this subject.

22.4 Do beta-blockers or digoxin affect PH associated with left heart disease? – Mehmet Serdar Küçükoğlu

Beta-blocker therapy is one of the basic treatment options in left HF. However, evidence concerning their use in right HF is not very clear. Beyond that, their use is not recommended because of their possible unfavorable effects on hemodynamics and exercise capacity. There are studies reporting that discontinuing propranolol has favorable effects in 10 patients with portopulmonary hypertension (197). Nevertheless, new data has shown that these drugs can be used safely in right HF and may prevent remodeling that may form in the right heart (198, 199). However, more trials are required about this subject.

It has been demonstrated that digoxin increased cardiac output in acute use. However, the efficacy of this treatment is not known in chronic administration. Digoxin can be administered to slow ventricular rate in PH with atrial tachyarrhythmia (200).

23.0 Treatment in isolated right HF – Mehmet Serdar Küçükoğlu

23.1 Should ACEIs/ARBs, beta-blockers, or MRAs be administered to patients with normal left ventricular ejection fraction?

The sympathetic nervous system and RAAS are activated in HF to compensate for cardiac output. However, chronic activation of these systems causes HF to progress by causing pathological remodeling of the heart (120, 201). Therefore, ACEI (or ARB), BB or MRA combination blocking neurohormonal and sympathetic activation constitutes the basis of HF treatment. It is known that these systems are activated in right HF as well (202). For example, it has been observed that plasma epinephrine levels were elevated, beta-1 adrenergic receptors were "down-regulated" in RV and heart rate variation was reduced in right HF (203-206). There are also trials demonstrating that RAAS is similarly activated (207, 208). However, there are very few trials that are conducted regarding the effect of treatments in right HF targeting these systems. For example, So et al. demonstrated that BB use did not cause any side effects in patients with PAH (199). The results of ongoing trials with bisoprolol and carvedilol in patients with PAH are expected to have an answer on this issue (209). There are trials showing that aldosterone levels are also increased in patients with PAH (210). In the ARIES Trials investigating the efficacy of ambrisentan in PAH, it has been reported that a more favorable improvement was observed in the group of patients receiving spironolactone with no deaths (211). There is need for more prospective randomized trials in this regard as well.

Consequently, it may be considered that sympathetic system and RAAS are activated in isolated right HF. And although there are limited trials concerning the benefit of suppression of these systems with ACEIs (or ARBs), BBs and MRAs, they may be used in treatment considering that the benefits received in left HF can be achieved in this regard as well.

23.2 How should diuretics and nitrates be used?

Following fluid retention in decompensated right HF, elevation in central venous pressure, enlargement in liver due to congestion, ascites and peripheral edema may develop. There are no randomized clinical trials evaluating diuretics in isolated right HF as in left HF. Our clinical observations show that diuretic therapy provides significant symptomatic benefit in patients with congestion. Diuretic choice and dose in isolated right HF can be similar to those of left HF. However, caution is recommended concerning hypotension that may develop due to sudden preload reduction. Dose up-titration is recommended according to the diuresis response received with lower doses. In order to prevent the intravascular volume reduction that may cause prerenal failure, the monitorization of blood pressure, renal functions and blood chemistry is important (200).

There is no requirement, or enough evidence for, nitrate use. If it is to be used, caution is recommended due to hypotension and output reduction developed following preload reduction. Again, it should be kept in mind that concurrent use of these drugs with PDE-5 inhibitors may increase the risk of hypotension.

23.3 Does the treatment of isolated right HF associated with PH differ from left HF?

The treatment target in isolated right HF associated with PH is to reduce right ventricular afterload by reducing pulmonary pressure and pulmonary resistance. For this, the treatment of the cause leading to PH should be the basic target in treatment. Unfortunately, for now, we do not have enough evidence regarding which drugs will be beneficial in right HF associated with PH.

23.4 What should PAH-specific treatment be in right HF associated with PAH (Group-1 PH)?

In right HF associated with PAH, PAH-specific treatment is applied as recommended in the PH guidelines (200). PAH-specific drugs are successfully used in patients with right HF with their RV afterload reducing effects. Although all of PAH-specific drugs are pulmonary vasodilators, only the effect of PDE-5 inhibitors have been shown on RV. Nagendran et al. demonstrated that PDE-5 expression increased in the myocardium of patients with right ventricular hypertrophy (RVH) and in the experiments of mice with RVH (212). It has been reported that PDE-5 inhibition caused an increase in RV contractility and a reduction in RV afterload in patients with RVH (200). Intranuclear receptors which are gene expression modulators in prostacyclin, another drug used in PAH treatment, can act as a ligand to PPARβ/δ. The protective effect of PPARγ agonists has been observed in mice monocrotaline and chronic hypoxic PH models by reducing pulmonary vascular remodeling. It has been observed that PPARβ/δ agonists reduced RVH and RV systolic pressure in hypoxia-related PH mice models with no effect on vascular remodeling in this model (213).

24.0 Drug treatment in anemia – Timur Selçuk

24.1 What are the differences between Anemia and Iron Deficiency in HF?

The incidence of anemia in HF reported to be 17% to 22% according to various studies. The incidence increases up to 40% in the registry studies. Incidence of anemia shows an increase in line with the worsening NYHA functional class as well (214-216). The prevalence of iron deficiency in HF has been detected to be between 5-21% in various studies (216-218). In 43% of anemic patients, serum iron or ferritin levels were low; whereas the ratio of microcytic anemia was only 6% (219). In a small study conducted in 73% of the advanced HF patients with anemia and normal serum iron, ferritin, and erythropoietin levels, iron deficiency has been demonstrated in the bone marrow (220). Serum ferritin levels are low in only a small number of HF patients with iron deficiency (221). It can be explained with the fact that iron is not sufficiently presented to the bone marrow in HF, hence accumulates in the reticuloendothelial system and although iron and ferritin levels in blood are in normal or high levels, iron deficiency is observed more frequently in patients with HF accompanied by anemia.

24.2 Should Anemia/Iron Deficiency be treated with drug therapy in HF?

The European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic 2012 state that iron deficiency is a frequent comorbidity and iron deficiency may cause muscle dysfunction and anemia in patients with HF. The guidelines recommend that in the evaluation of patients with suspected HF, iron deficiency should be investigated by measuring ferritin and transferrin saturation levels (Figure 4). However, these measurements have not been accepted as a stan-

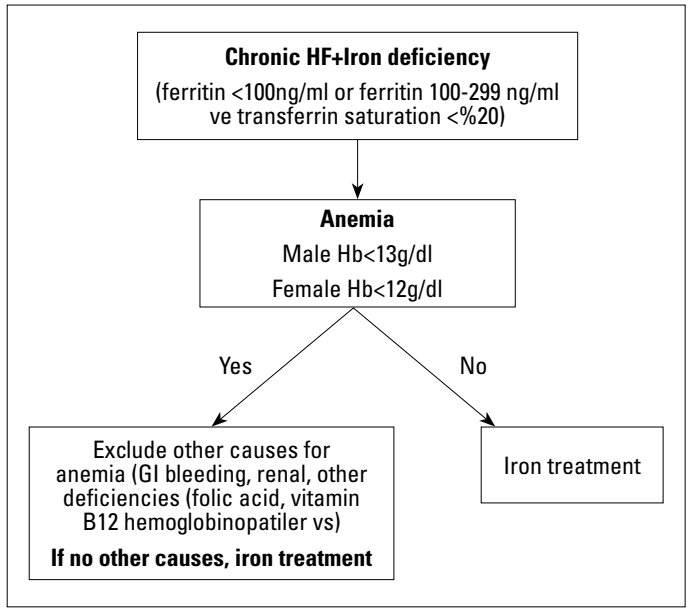


Figure 4. Management of anemia/iron deficiency in HF

dard procedure yet. Iron therapy should be initiated regardless of presence of anemia if there is iron deficiency in patients with HF. If erythropoietin treatment is indicated in patients with HF, particularly in patients with renal dysfunction, concurrent iron therapy may be important due to increased iron need. In anemia not caused by iron deficiency, treatment strategy may change according to the etiology of anemia.

24.3 What are the agents that can be used in the treatment and what are the routes of administration?

Current data does not support the use of agents which stimulate erythropoiesis in the treatment of mild and moderate anemia observed in patients with HF. In the studies conducted up to now, it has been demonstrated that, in patients with HF, use of agents which stimulate erythropoiesis does not provide any clinical benefit, in contrast, they increased thromboembolic adverse events (222).

It is essential to determine the cause of anemia in HF (e.g. iron deficiency, vitamin B12 deficiency, folic acid, bleeding, renal failure, etc.) and provide etiology-specific treatment. Iron absorption is generally poor in oral iron treatment. Furthermore, gastrointestinal side effects are observed in 60% of the patients receiving oral iron therapy. These problems further increase due to a reduction in gastrointestinal absorption in HF. There is lack of evidence regarding the clinical benefit of oral iron administration in the treatment of iron deficiency. In addition, it has been shown that IV iron administration improved exercise capacity, cardiac functions, symptoms and quality of life (223, 224). Therefore, IV administration of iron in iron deficiency seems to be more rational in HF. However, risk of allergy and infection should be considered in IV iron therapy.

Blood transfusion is not recommended in HF with the exception of acute and symptomatic anemia. Blood transfusion has a very limited use due to its risks and its limited beneficial effect. If necessary, the volume status of the patient should be monitored carefully during blood transfusion.

25.0 Treatment in HF-PEF – Dilek Ural

25.1 Do ACEIs/ARBs have a place in the treatment of HF-PEF?

On the contrary to HF-REF, the role of ACEIs or ARBs in HF-PEF patients is not clear. Major randomized, controlled clinical trials conducted with ACEIs and ARBs to date and their results are summarized in the Table 37. Although the favorable effects of ACEIs and ARBs on mortality in HF-PEF have been noted in observational studies, meta-analyses of randomized, controlled trials did not reveal any effect on all-cause mortality or other cardiovascular events (225-227). However, hospitalization due to HF reduced slightly (RR 0.88, 95% CI 0.80-0.97). The Swedish Heart Failure Registry data (228), which was published in 2012 and included >16,000 patients with diastolic HF, indicated that mortality benefit could be achieved in patients receiving >50% of the target dose of ACEIs or ARBs. On the basis of these evidences, main indication for using ACEIs or ARBs in HF-PEF is the treatment of comorbid conditions such as hypertension, diabetes, proteinuria, etc.

25.2 How should diuretics be used in HF-PEF?

Congestion in HF-PEF develops due to increase in pulmonary capillary wedge pressure (PCWP) and subsequent PH and right HF, regardless of an increase in PCWP. Therefore, diuretic therapy is used to control fluid and sodium retention and to relieve shortness of breath and edema, as in patients with HF-REF. Randomized, controlled trials cannot be conducted with diuretics since they do not have an alternative to improve congestion. In the Hong Kong Diastolic Heart Failure Study, which investigated the effect of diuretics alone or combined with irbesartan or ramipril in HF-PEF, symptoms and exercise capacity improved in all three treatment groups and no further benefit was shown with the addition of ACEI or ARB (229). Nevertheless, after one year treatment, both left ventricular function and NT-proBNP values improved in patients using diuretics with ACEI or ARB.

In ACCF/AHA guidelines, diuretic therapy is recommended as Class I indication in patients with HF-PEF who have symp-

Table 37. Major randomized, controlled clinical trials with ACEIs and ARBs in HF-PEF

	Trial drug	Number of patients (n)	Follow-up time (year)	Result
Trials with ACEIs				
PEP-CHF	Perindopril 4 mg o.d.	850	2.1	Perindopril did not reduce cardiovascular death in elderly patients with chronic HF, however, reduced HF hospitalization and increased exercise capacity
Trials with ARBs				
CHARM	Candesartan 32 mg o.d.	3023	3.1	Candesartan did not reduce cardiovascular death, however, a slight reduction was detected in HF hospitalization
I-PRESERVE	Irbesartan 300 mg o.d.	4128	4.1	No reduction was detected in death or cardiovascular hospitalization

ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; HF-PEF – heart failure with preserved ejection fraction

toms due to congestion. Aggressive and long-term diuretic therapy may cause postprandial or orthostatic hypotension or even syncope, particularly in elderly patients with HF-PEF. Therefore, discontinuation of diuretic treatment in patients without overt clinical congestion and close monitoring of symptoms may affect hemodynamics more favorably by preserving intravascular volume and preload (230, 231).

25.3 Is beta-blocker treatment beneficial in HF-PEF?

There is no consensus on the effect of BBs in HF-PEF patients. Theoretically, tachycardia may cause an increase in HF symptoms by leading to shortening of diastolic time. However, if there is no tachycardia, reducing the heart rate may cause prolongation of diastasis by leading to chronotropic incompetence. In this circumstance, it is wiser not to use BBs.

Due to impairment of diastolic function in HF-PEF, increase in cardiac output during exercise becomes largely dependent on heart rate in these patients. BBs may inhibit cardiac output elevation by preventing physiological heart rate increase during exercise. Therefore, in patients with symptomatic worsening after BB initiation, it may be necessary to discontinue BBs.

Although some observational studies, registries and their meta-analyses, have shown a reduction in all-cause mortality with BBs, such an effect was not detected in two relevant randomized, controlled trials (subgroup analysis of the SENIORS and J-DHF trials) (Table 38) (13, 232-234). Similarly, symptoms or exercise capacity have not improved in the ELANDD Trial conducted with nebivolol. Therefore, the main indications of BBs in HF-PEF can be summarized as management of accompanying hypertension, ischemia, and arrhythmias.

25.4 Should MRAs be used in HF-PEF?

In HF-PEF pathogenesis, MRs activated by aldosterone involve in the formation of cardiac remodeling via sympathetic activation, cardiac and vascular fibrosis, endothelial dysfunction, sodium retention and potassium loss and diastolic dysfunction. Therefore, the opinion that MRAs may have a favorable effect on HF-PEF is commonly accepted. The general conclusion of randomized, controlled trials conducted to test this hypothesis is that although MRAs did not have any effect on mortality, they reduced HF hospitalization, improved quality of life and, partially, cardiac remodeling as well as diastolic dysfunction. Recently, a meta-analysis that evaluated 14 randomized, controlled trials including Aldo-DHF (235) and TOPCAT (236) studies, no reduction has been demonstrated in all-cause mortality, (237) but the ratio of hospitalization reduced significantly (RR 0.83; p = 0.03). However, when the results from Russia and Georgia were excluded from the TOPCAT Trial, a significant reduction has been detected in the combined end-point comprised of hospitalization related to cardiovascular mortality, cardiac arrest or HF (RR 0.85; 95% CI 0.74-0.96; p = 0.01).

Among current therapies, MRAs appear to be the most preferable agents in patients with HF-PEF. Spironolactone 25-50 mg daily or eplerenone 25 mg daily were widely used in the trials. If MRAs are to be preferred, caution is recommended against creatinine and potassium elevations, particularly in elderly patients. Incidence of renal failure is 1.91% and increase in potassium level >5.5 mmol/L is 12.15% in the meta-analyses of trials. Furthermore, gynecomastia that may develop due to spironolactone (2.8%) may be disturbing for patients.

25.5 Can digoxin be beneficial in HF-PEF?

The major studies investigating the role of digoxin in HF-PEF are the subgroup analysis of Digitalis Investigation Group (DIG) Trial (DIG-PEF) (238). In this trial, digoxin did not change mortality in patients with preserved EF (EF >45%), slightly reduced HF hospitalization (HR 0.79; 95% CI, 0.59-1.04; p=0.094), however, increased unstable angina-related hospitalization (HR 1.37; %95 CI 0.99-1.91; p=0.061). In another subanalysis of the trial, 30-day all-cause hospitalization increased significantly in elderly patients (≥65 years) using digoxin (HR 2.46, 95% CI 1.25-4.83; p=0.026) (239).

For now, the only indication for using digoxin in HF-PEF is to control ventricular rate of AF.

25.6 Can calcium channel blockers be used in HF-PEF?

Calcium is the major electrolyte that contributes to the active relaxation phase of diastole. Therefore, CCBs have been considered as favorable drugs in diastolic HF in the past years. In two small scale studies, the rate-limiting CCB verapamil could improve exercise capacity and symptoms (240, 241). Despite the lack of major randomized clinical trials relating this topic, a large registry study performed in hospitalized elderly patients was not able to show a change in total mortality or rate of HF hospitalization with prescriptions of CCBs, regardless the type of the CCB (242). Currently, the main indications of use for CCBs

Table 38. Main randomized, controlled clinical trials conducted with beta-blockers in HF-PEF

	Trial drug	Number of patients (n)	Follow-up time (year)	Result
SENIORS	Nebivolol 1.25-10 mg o.d.	643	1.75	No reduction was observed in all-cause mortality or cardiovascular hospitalization
J-DHF	Carvedilol 2.5-20 mg o.d.	245	3.2	No reduction was observed in cardiovascular mortality or hospitalization, however, in patients receiving the drug above the median dose (>7.5 mg daily), the time to initial occurrence of events prolonged

in HF-PEF patients is rate control in AF (rate-limiting CCBs), treatment of hypertension and myocardial ischemia.

25.7 Which drugs are effective in symptom control in patients with HF-PEF?

The HF-PEF patients represent a quite heterogeneous group. The treatment should therefore be individualized according to each patient. The main treatment that has been shown to reduce symptoms is exercise (243). In a recent meta-analysis of 6 randomized, controlled trials, it has been demonstrated that exercise did not have a significant effect on echocardiographic variables, whereas, increased cardiorespiratory fitness and quality of life significantly (244). Therefore, exercise/rehabilitation programs should be recommended to all patients who are clinically eligible.

Major pharmacological agents which have been shown to improve quality of life are MRAs. Diuretics are used to control fluid and sodium retention and to relieve shortness of breath and edema. Efficient treatment of hypertension, myocardial ischemia, and ventricular rate control in AF patients are considered important.

25.8 Which drugs are effective in reducing re-hospitalization in HF-PEF?

The major pharmacological agents that can reduce re-hospitalization due to HF in patients with HF-PEF are renin-angiotensin-aldosterone system blockers and MRAs. In the PEP-CHF Trial, it has been reported that significant improvement was achieved in 1-year HF hospitalization and 6-min walk test with perindopril; however, it has been reported that these improvements lost their significance at the end of 3 years due to potential treatment discontinuation and substantial cross-over. In the CHARM-Preserved Trial, there was a significant reduction in HF hospitalization and the ratio of patients hospitalized alone with candesartan. Although the results of the TOPCAT Trial have suggested that spironolactone was not different from placebo regarding primary end-points (cardiovascular mortality, HF hospitalization and resuscitated cardiac arrest), they have shown that it improved HF hospitalization alone significantly.

Administering diuretics at a dose which will keep the patient in dry weight may also be beneficial in reducing re-hospitalization.

25.9 How important is the control of comorbid conditions in HF-PEF?

Since HF-PEF patients are generally at advanced age, almost every patient has at least one accompanying disease and most of them have multiple co-morbidities (Figure 5) (245, 246). These diseases are important as they have to be considered in the differential diagnosis of HF-PEF, increase mortality and morbidity of HF, interfere with the treatment, and cause recurrent hospitalizations if diagnosis cannot be established (247). Therefore, the patient should be considered as a whole, accompanying pathologies should be detected and managed (248). The ideal solution for elderly patients with HF-PEF appears to be following of the patients by multidisciplinary geriatric clinics offering rehabilitation programs.

25.10 Are there any promising novel drugs in the treatment of HF-PEF?

Although HF-PEF is a complicated disease with concurrent pathologies of different phenotypes, the basic problem is considered to be in the structure of extracellular matrix of myocardium. In many studies, disorders in fibrosis, collagen-I/III, titin, matrix metalloproteinases, TIMPs, fibrillin, fibronectin, vitronectin, cytokines, and galectin-3, etc. were examined and new treatment targets were investigated. Recently, the importance of endothelial dysfunction has become more prominent. However, the absence of a generally accepted definition for HF-PEF and inability to constitute a clear experimental model make drug researches difficult.

Novel drugs under investigation and drugs with ongoing clinical trials are listed in the Table 39 (249). Interventional treatments other than pharmaceutical therapies may also be effective in improving the HF-PEF symptoms. Recently, attempts were made to reduce left atrial pressure by forming a small interatrial shunt through a catheter and as a result of favorable findings in preliminary studies, long-term follow-up studies were initiated (250). Atrial pacing and renal denervation are other interventional treatment methods under investigation.

26.0 Heart failure therapy in patients with advanced heart failure – Jean Marc Weinstein

26.1 Intermittent inotropic support in symptomatic HF patients with severely depressed LV function: Is it helpful or harmful?

Fifty per cent of patients with advanced HF will die within a year. Many attempts have been made to improve the survival of this group of patients, amongst them inotropic agents.

These drugs, when used intravenously, (such as dobutamine, dopamine, milrinone, levosimendan) are generally used in the context of an acute decompensation of HF in patients with reduced ejection fraction (HFrEF), in whom haemodynamic compromise accompanies the congestion (251). Inotropic therapy has class IIa,C recommendation according to the ESC guidelines, (3), class I, C recommendation according to ACCF/AHA guidelines (4), "May be considered", C recommendation according to HFSA guidelines (252). Under these circumstances, the treatment is limited to a few days only.

Patients with severe HF awaiting heart transplantation or definitive mechanical support (such as left ventricular assist devices, LVADs), may need to be maintained on longer-term inotropic support with one or more of these agents (IIa, B recommendation according to ACCF/AHA guidelines (4). In addition, these inotropic drugs can be used as short-term haemodynamic support in hypotensive HFrEF patients, or long-term use as pal-

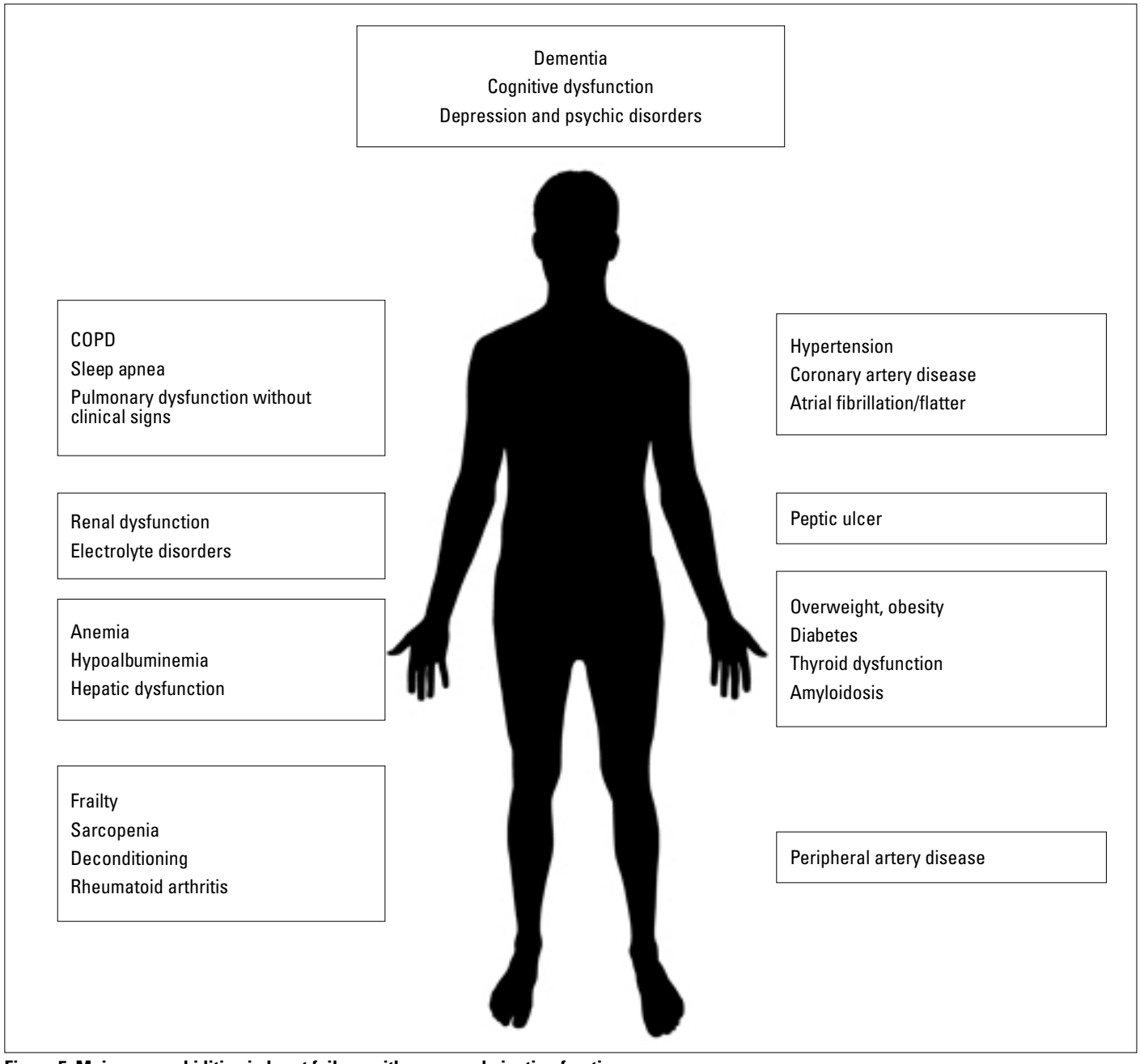


Figure 5. Major co-morbidities in heart failure with preserved ejection fraction

liative care in patients not eligible for transplantation or LVAD (IIb, B recommendation according to ACCF/AHA guidelines (4).

The long-term intermittent use of IV inotropes is not recommended, from a safety and an efficacy point of view (III-Harm-, B recommendation according to ACCF/AHA guidelines (4), if used for reasons other than palliative care.

On the other hand, evidence is accumulating of safety and efficacy in using these powerful agents, when lower doses are used, with careful monitoring.

Freimark et al. (253) presented a single-center 5-year follow-up of patients with severe HF in a dedicated HF day-care setting. The patients were treated with IV diuretic combinations together with intermittent low dose (≤5 μg/kg/min) dobutamine, and/or low dose (≤3 μg/kg/min) dopamine, as well as other agents. The observed 29% annual mortality rate was significantly lower than that reported in the literature (50%). Similarly, the hospital admission rate was also remarkably low (0.6 hospitalizations/patient/year) compared to that reported in the literature.

Several small studies have been performed, using intermittent infusions of inotropes such as dobutamine or milrinone. However, no conclusions on mortality are possible as patient selection and infusion drugs, as well as protocols, were not standardized (254). In Guglin & Kaufman's review (254) of parenteral inotropic studies, they propose that the excess mortality dem-

Table 39. Novel drugs in heart failure with preserved ejection fraction

	Drug	Trials (Phase)	Results
RAAS antagonists			
Direct renin inhibitors	Aliskiren	ALLAY	Left ventricular hypertrophy reduced in a ratio similar to that of losartan
AT1 and neprilysin inhibitor (ARNI)	LCZ696	PARAMOUNT II (Phase II)	There was more reduction in NT-pro BNP than valsartan alone
		PARAGON (Phase III)	Ongoing
cGMP-PKG pathway			
Selective PDE inhibitor	Sildenafil	SIDAMI	There was no change in the left and right ventricular hemodynamics with sildenafil after AMI
		RELAX	Effort capacity did not change after 24 weeks
Soluble cGMP stimulation	Vericiguat	SOCRATES (Phase III)	Ongoing
	Riociguat	DILATE (Phase IIb)	Favorable hemodynamic effects were observed
If channel blocker	Ivabradine	EDIFY	Ongoing
Endothelin receptor blockade			
	Bosentan	BADDHY (Phase III)	
Ca2+ cycle			
NCX reverse mode blocker	SEA0400	Experimental	
RyR2 stabilization	K201 (JTV519)		
SERCA2-mediated Ca2+ sequestration	BH4	Experimental	
NO pathway			
NOS coupling	BH4	Experimental	
Nitrates	Isosorbide-mononitrate	NEAT	Ongoing
Cytokines			
Recombinant IL-1 receptor antagonist	Anakinra	D-HART	Favorable improvement was observed in aerobic exercise capacity

AT1 – angiotensin 1 receptor; BH4 – tetrahydrobiopterin; cGMP – cyclic guanosine monophosphate; IL-1 – interleukin-1; NCX – sodium-calcium exchanger; NO – nitric oxide; PKG – protein kinase G; RAA – renin angiotensin aldosterone; RyR2 – Ryanodine receptor 2

onstrated in some of the trials, results from certain common features: they were performed with inotropic agents not currently in use; they were performed before automated cardioverter-defibrillators were standard care for primary prevention; and they were performed on patients without evidence of low output HF and without indications for inotropes. As a result, these studies may not be applicable to current practice.

Recently, a panel of experts has reviewed the use of intermittent levosimendan therapy (255). Over 500 patients have been included in studies with repetitive use of this drug in patients with chronic advanced HF. There were disparities in patient selection, in study design and in follow-up, so that comparison between the trials and definite conclusions are difficult. However, the benefits of the repetitive use of levosimendan have been demonstrated, including improved haemodynamics, symptoms, rehospitalisation rates, and biomarkers. The issue of mortality, however, is unresolved, and requires further studies.

26.2 Is there any role for pharmacological therapy in reducing the severity of mitral regurgitation?

In patients with acute mitral regurgitation (MR), filling pressures can be reduced with nitrates and diuretics. Reduction in afterload and in regurgitant fraction can be obtained with sodium nitroprusside or an intra-aortic balloon pump. Inotropic drugs and an intra-aortic balloon pump should be added in case of hypotension (256).

As vasodilator therapy helps in acute severe MR, intuitively it seems reasonable to use afterload reduction in chronic asymptomatic MR with normal left ventricular (LV) function in an attempt to delay the need for surgery. However, the few trials investigating this therapy have demonstrated little or no clinical benefit. Thus, in asymptomatic, normotensive patients with chronic significant MR and normal ejection fraction (EF), there is no evidence to support the use of vasodilators, including ACEIs, and they are therefore not recommended in these patients (256,

257). Indeed, as vasodilators decrease LV size and mitral closing force, they may worsen MR rather than improving it. In patients with hypertension, on the other hand, the hypertension must be controlled because of its associated morbidity and mortality and also because it increases LV systolic pressure and worsens MR.

AHA/ACC 2014 guidelines: CLASS III, No benefit, vasodilator therapy is not indicated for normotensive asymptomatic patients with chronic primary MR (stages B & C1) and normal systolic LV function, (Level of Evidence: B)

Patients with MR may eventually develop myocardial damage, LV dysfunction and HF. Surgery is usually indicated once this stage is reached. However, in patients in whom surgery is not performed or is delayed, medical therapy for systolic dysfunction should be commenced. There is little evidence available specifically for patients with MR and LV dysfunction, but the accepted treatment for HF is recommended, including beta blockers, ACEIs or angiotensin receptor blockers (ARBs), and MRAs. Beta blockers have been shown to reverse LV dysfunction in experimental MR, and patients receiving theses agents may have better surgical outcomes and delayed onset of LV dysfunction compared with those not taking them (3, 256, 257).

AHA/ACC 2014 guidelines: CLASS IIa, medical therapy for systolic dysfunction is reasonable in symptomatic patients with chronic primary MR (stage D) and LVEF less than 60% in whom surgery is not contemplated (Level of Evidence: B).

Chronic MR commonly develops as a result of severe LV dysfunction, especially when accompanied by LV dilation. In these patients, standard HF therapy is called for, including diuretics, beta blockers, ACEIs or ARBs, and MRAs. These drugs improve prognosis and/or symptoms in HF and probably when HF is also complicated by chronic secondary MR (3, 257).

AHA/ACC 2014 guidelines: CLASS I, patients with chronic secondary MR (stages B to D) and HF with reduced LVEF should receive standard GDMT therapy for HF, including ACEIs, ARBs, beta blockers, and/or aldosterone antagonists as indicated (Level of Evidence: A).

26.3 How to manage evidence-based therapy in hypotensive advanced heart failure patients

Hypotension in occasionally seen in patients with advanced heart failure with reduced ejection fraction (HFrEF) and is estimated to be present in 5-10% of chronic HF patients. It may be the result of pump failure itself, or due to drug side-effects, since most of the evidence-based drug therapy (EBDT) involves agents that may lower blood pressure (BP), such as ACEI, ARBs, or beta-adrenoceptor blockers (BB). The finding of significant hypotension is very often an ominous sign, portending a poorer prognosis. Several questions arise when dealing with such patients (258).

1. First of all, can a reversible cause be identified and corrected? Several situations may result in hypotension in HF patients, such as non-cardiac problems, including gastrointestinal bleeding, sepsis, autonomic dysfunction, dehydration or concomitant treatment with medications that may lower blood pressure. Cardiac problems causing hypotension include ischaemic episodes or arrhythmias. All of these need to be excluded or treated before changing HF treatment regimens. Medications that may exacerbate hypotension include nitrates, CCBs, alpha-adrenoceptor antagonists, PDEI-5 inhibitors and certain psychiatric agents. If possible, these drugs should be stopped.

2. Secondly, can EBDT be commenced (if the patient is not yet receiving it)? It should be stressed that in patients with advanced HF, low BP (as long as systolic BP remains over 80 mm Hg), is not a contraindication to commencing or uptitrating EBDT. It is often the case that on initiating therapy or on increasing the doses, patients may experience some lightheadedness or dizziness during the first couple of days, but this almost invariably resolves. Once the patient's BP stabilizes, further uptitration is usually continued, albeit usually at a slower rate and with smaller increments than used in patients with a higher BP.

3. Once EBDT is started, in order for titration to be performed, which drugs should be given, in which order, and at what dosages? It is generally recommended to start therapy with ACEI before BB (3), although it also acceptable to commence in reverse order (59). The decision as to which drug to initiate first in hypotensive HF patients may be made on an individual basis. For example, in patients with significant tachycardia, or with a basis of ischaemia, it may be more appropriate to start a BB and then add ACEI. In addition, thought should be given to the BB used, thus beta-1 selective antagonists such as metoprolol may have a less marked hypotensive effect than carvedilol, which also has alpha-adrenoceptor antagonist activity.

When commencing treatment with ACEI in hypotensive patients, it may be appropriate to use a short-acting drug such as captopril, which could enable more flexibility with uptitration.

EBDT stresses reaching evidence-based doses, although in the real world, this is often impossible to achieve for various reasons (such as low BP or significant bradycardia). The question also arises as to whether to increase the dose of the first drug to recommended target levels before starting the next drug. In general, whichever agent is chosen first, it is gradually increased and then the next drug is commenced, with a continual increase in parallel to reasonable intermediate doses. In these patients, usually the maximal doses attained are lower than the recommended targets. Some practical points may help, for example titrating at longer intervals and in smaller doses than usually accepted. Another useful tip is to advise the patient to take the medications separately and not together, and also separately from diuretics.

In asymptomatic patients with significant hypotension, the low BP itself is not an indication to discontinue or reduce doses of the important drugs such as ACEI or BB. Only in patients developing shock or signs of end-organ damage do these drugs may need to be temporarily stopped or their doses reduced, bearing in mind that this in itself may cause a deterioration in the patient's state.

A possible solution?

A recent study described a small group of patients with HFrEF and symptomatic hypotension precluding optimal medical

therapy, who were started on midodrine, a peripheral alpha-1 adrenergic agonist. More patients on this drug reached higher doses of EBDT, resulting in greater improvements in EF and clinical outcomes, such as reduction in hospital admissions, compared to patients not receiving it (259).

26.4 How to Treat Hyponatraemia in patients with refractory congestion

Hyponatraemia has been recognized for many years as a powerful adverse prognostic factor in heart failure (HF) patients. For example, in the Organized Program To Initiate Life-Saving Treatment In Hospitalized Patients With Heart Failure (OPTIMIZE-HF) study, which included data on 47 647 admissions for acute decompensated HF (ADHF), almost 20% of the patients presented with hyponatremia, defined as a serum sodium level<135 mEq/L (260). These patients had significantly worse outcomes and were more likely to require dialysis or inotropic drugs. Their in-hospital mortality was also significantly higher compared with patients with normal serum sodium levels (6% vs 3.2%, $p < 0.0001$). Almost half of the study population had preserved LVEF, implying that hyponatremia is an independent predictor of outcomes in HF patients with both preserved, as well as reduced, LVEF (261).

Causes of hyponatraemia in HF

Dilutional: In patients with HF, the reduced cardiac output and blood pressure result in a drop in perfusion pressure, sensed by the carotid sinus baroreceptors and the afferent renal arterioles. This causes the release of hormones, all of which attempt to correct the lower perfusion. Thus, renin secretion by the kidneys leads to sodium (and therefore water) retention. Renin rise also stimulates the increase in angiotensin II and aldosterone (the RAAS). Angiotensin II and noradrenaline (secreted by the sympathetic nervous system in response to the lowered baroreceptor perfusion), both reduce renal perfusion which further increases sodium and water reabsorption. In parallel, angiotensin II stimulates the secretion of antidiuretic hormone (ADH, also called arginine vasopressin – AVP) from the posterior pituitary, which restricts the kidney's secretion of free water. The end result of these interacting mechanisms is salt and fluid retention, worsening the oedematous state. Despite this increased volume state, reduced perfusion pressure on the baroreceptors and kidneys causes the body to perceive volume depletion, thereby perpetuating the vicious cycle. In addition, angiotensin II and reduced cardiac output both stimulate thirst, causing increased water intake. Hyponatraemia associated with HF is generally in hypervolemic patients. There is a disproportionate retention of both sodium and water, with the increased body fluid volume exceeding that of total sodium content, resulting in dilutional low serum sodium concentration.

Depletional: This situation is more common in acute gastrointestinal or third-space losses, clinical signs of hypovolemia, and recent use of diuretic agents—especially at high doses or in combination therapy (90).

Hyponatraemia often develops insidiously in patients with chronic HF, often to mild levels only, unless provoked to much lower levels by an additional acute factor such as increased diuretic use or diarrhea. Mild hyponatraemia may be asymptomatic or cause minimal neurological symptoms. The development of severe hyponatraemia (<125 meq/l), in contrast, is extremely dangerous, resulting in severe neurological symptoms, particularly when the onset is fast. To compound matters, the correction of this state has to be managed with extreme caution, as the correction itself, if performed too quickly, may also cause irreversible brain damage in the form of central pontine myelolinysis.

Approach to treatment of hyponatraemia

To start with, a careful history, physical examination and laboratory tests will aid in excluding non-cardiac causes such as diarrhea, drug-induced hyponatraemia or significant hyperglycaemia.

Depletional: In cases with a clear history of volume depletion, infusing isotonic saline will raise the serum sodium levels to normal. In addition, replenishment of potassium and magnesium stores will assist in the correction of hyponatraemia.

Dilutional: Treatment of this state is based on fluid restriction (1.5-2 litres a day, IIa, C recommendation by ACCF/AHA) (4), and the use of diuretics together with the simultaneous infusion of saline, all under careful clinical and biochemical monitoring. In terms of diuretic use, IV loop diuretics are the recommended treatment. Acetazolamide may be used instead of, or as well as, loop diuretics, but not thiazides or MRAs, which may worsen the hyponatraemia (and may have contributed to its onset in the first place). In terms of saline use, in general isotonic saline is administered, although recent reports of the use of hypertonic saline seem promising.

Renin angiotensin aldosteron system blockers (ACEI, ARBs) increase renal blood flow and decrease proximal tubular sodium reabsorption, thus they have an important role in normalizing the serum sodium level.

AVP (ADH) receptor antagonists

There are several AVP receptors, including V1a, V1b and V2 receptors. The V2 receptors are mainly responsible for the antidiuretic response, while V1a receptors are involved in vasoconstriction and V1b in release of adrenocorticotropic hormone. The AVP receptor antagonists produce a selective free water diuresis without affecting sodium and potassium excretion, which will tend to correct the hyponatremia.

Oral AVP antagonists include tolvaptan, satavaptan and lixivaptan, which are V2 selective blockers. Conivaptan is an IV V2 and V1a blocker. Tolvaptan and conivaptan are approved for use in the USA for treating hyponatraemia in HF. One problem with these agents is an increase in thirst, and the additional oral fluid intake may negate the gains made in water excretion.

In patients with congestive HF, hyponatraemia and significant renal dysfunction, renal replacement therapy (such as haemodialysis) may be necessary in removing excess fluid and aiding in correcting the hyponatraemia.

27.0 Drug therapy management in HF: Cases from real life clinical practice

CASE-1

Drug therapy management in a HF patient with renal dysfunction and anemia – Sinan Aydoğdu

Summary: Drug therapy management in a patient with newly diagnosed HF who is symptomatic with BP 135/85 mm Hg, heart rate 86 b.p.m. in sinus rhythm, in NYHA Class III, with LVEF 22%, NT-proBNP 11,200 pg/mL, creatinine 1.9 mg/dL, potassium 4.8 mEq/L, Hb 10.4 g/dL, and ferritin 80 µ/L.

Case: A 65-year-old male patient presented to our clinic with the complaints of dyspnea on effort which have gradually increased for about a month, fatigue and swelling in legs. The patient's history revealed that his dyspnea on effort started approximately 3 months before; however, for the last one month he could not perform activities requiring even a mild effort and had difficulty in sleeping (NYHA Class III). The patient had no anginal complaints and stated that he had no regular use of drugs, only received NSAIDs and vitamins intermittently and he was initiated on medical treatment with the diagnosis of HT approximately 5 years ago but did not receive his antihypertensive medications. BP was 135/85 mm Hg and pulse was regular and 86 b.p.m. Cardiac sounds were rhythmic, S3+ and systolic 2/6 murmur was heard at mitral focus. Crepitant rales were present in the basal and 1/3 mid segments of lungs bilaterally on respiratory examination. There was jugular venous distension and ++ pitting edema in bilateral lower extremities. Sinus rhythm was observed in ECG. Hemoglobin (Hb) was measured as 10.4 g/dL and ferritin as 80 µ/L and other whole blood parameters were within normal limits. Blood chemistry results were: fasting blood glucose 96 mg/dL, potassium: 4.8 mEq/L, sodium: 138 mEq/L, serum creatinine: 1.9 mg/dL and NT-proBNP: 11.200 pg/L. Transthoracic echo findings were: left ventricular end-diastolic diameter (LVEDD): 65 mm, LVEF: 22%, septal / posterior wall thicknesses: 6 mm/7 mm and left atrial diameter: 48 mm. Left ventricular wall motion was globally and severely hypokinetic and he had moderate mitral regurgitation and mild tricuspid regurgitation. Systolic pulmonary arterial pressure (sPAP) estimated by tricuspid regurgitant flow was 36 mm Hg.

HF signs and symptoms, reduced LVEF and NT-proBNP of > 300 pg/L in patient who had not received HF diagnosis allowed us to establish the diagnosis of HF. Briefly, according to physical examination, laboratory and imaging findings, our patient had newly diagnosed HF-REF accompanied by renal failure and anemia.

In the management of drug therapy of such a patient, renal dysfunction and anemia should be monitored carefully. The causes for renal dysfunction may be renal diseases, renal congestion, use of ACEI/ARB or MRAs, NSAIDs or other nephrotoxic drugs or dehydration. Our patient should be evaluated with regard to these factors. Anemia is an unfavorable prognostic marker in patients with HF.

Reducing symptoms, improving quality of life and decreasing hospitalization by increasing survival in the long term should be the treatment targets for the patient. ACEI (if not tolerated, ARB) and BB therapy should be initiated in our patient as with all patients with LVEF <40%. Absolute contraindications for ACEIs are bilateral renal artery stenosis, history of angioedema and pregnancy. There is no absolute contraindication in case creatinine is >2.5 mg/dL and/or potassium (K) is >5.0 mEq/L; however, caution is recommended. Since K was <5 mEq/L and creatinine was <2.5 mg/dL in our patient, ACEI (if not tolerated, ARB) therapy should be initiated. The treatment should be initiated with the lowest dose and the dose should be titrated with at least 2 weeks' intervals and increasing to the maximum dose should be aimed. Blood chemistry should be repeated at 1-2 weeks after the initiation, 1-2 weeks after the last titration and every 4 months subsequently. Dose reduction is not necessary until creatinine increases up to 50% compared to baseline or is <3 mg/dL (the lower one is accepted) and/or serum K level is <5.5 mmol/L (Table 40). Supplemental drugs and diuretic therapy that may cause the increase in potassium should be discontinued and the patient should be monitored. If the increase in creatinine is persistent, the ACEI dose should be reduced and renal functions should be measured 1-2 weeks later. ACEI should be discontinued if increases in creatinine and potassium continue. ACEIs/ARBs should be discontinued if creatinine increases by 100% compared to baseline or is >3.5 mg/dL and/or K is >5.5 mEq/L (Table 40). BBs should be initiated in all HF patients with EF <40%. Since our patient had renal dysfunction, one of the beta blockers metabolized by liver should be preferred. Adding mineralocorticoid receptor antagonists (MRAs) to the treatment should be planned if the patient is still in NYHA Class II-IV despite ACEI and BB therapy. If creatinine is >2.5 mg/dL and/or K is >5.0 mmol/L, MRA use is not recommended. If the patient's baseline creatinine values are between 1.5 and 2 mg/dL in females and 2-2.5 mg/dL in males, MRAs are recommended to be initiated in the lowest dose. Therefore, in our patient, when starting MRA, daily doses of 12.5 mg for spironolactone and 25 mg for eplerenone should be initiated. The doses should be increased with 4-8-week intervals. Measurement of potassium and creatinine levels

Table 40. Renal Dysfunction-ACEI / ARB Use

ACEIs/ARBs	<50% increase in creatinine (<3 mg/dL) and/or K<5.5 mEq/L	50-99% increase in creatinine (<3.5 mg/dL) and/or K <5.5 mEq/L	>100% increase in creatinine (>3.5 mg/dL) and/or K >5.5 mEq/L
	Maintain the dose, prevent effects such as diuretics, potassium replacement, etc. that may cause an increase in potassium	Reduce the dose, prevent effects such as diuretics, potassium replacement, etc. that may cause an increase in potassium	Discontinue treatment

Table 41. Renal dysfunction - Mineralocorticoid receptor antagonists (MRA) use

MRAs	Creatinine <2.5-3.5 mg/dL) and/or K=5-5.5 mEq/L	Creatinine >3.5 mg/dL) and/or K >6 mEq/L
	Reduce the dose, monitor renal functions closely	Discontinue treatment

in blood chemistry in the first and 4th weeks following the MRA initiation and/or every dose increase is recommended. Subsequently, biochemical tests should be performed at weeks 8 and 12, at months 6, 9 and 12 and then every 4 months. MRA should be discontinued immediately if serum creatinine is >3.5 mg/dL and/or K is >6 mEq/L (Table 41). If serum creatinine is 2.5-3.5 and/or K is 5.5-6 mmol/L, it is recommended that the dose should be reduced and renal functions should be monitored closely. In the treatment of our patient, due to renal dysfunction, use of NSAIDs should be avoided and potassium supplements should be discontinued to minimize the potential increases in potassium and creatinine levels that may occur due to ACEI/ARB and MRA therapies.

Diuretic therapy should be planned in our patient due to congestion signs. The target of diuretic therapy should be to prevent the symptoms and signs of congestion and avoid unnecessarily prolonged diuretic use with fluid balance monitorization. Thus, worsening of renal dysfunction that may be caused by diuretic use can be prevented. Although diuretics ensure symptomatic relief, they do not affect in the rate of mortality and hospitalizations. Therefore, they should only be used in the presence of congestion. In cases when diuretic therapy is required to be administered due to congestion, if progressive worsening is observed in renal functions (creatinine >2.5 mg/dL), MRAs should be discontinued, if the loop and thiazide group of diuretics are co-administered, the thiazide group of diuretics should be discontinued, ACEI/ARB dose should be reduced and if there is no response with these precautions, hemofiltration/dialysis should be considered.

Another problem with our patient is anemia. Anemia is associated with functional worsening, increased risk of hospitalization and reduction in survival. Generally, the cause of anemia should be investigated even though no etiology could be determined. Treatable causes should be treated with a standard therapy. In patients in whom the cause cannot be detected, treatment of iron deficiency anemia with i.v. iron preparations is recommended. Although it does not take a place in treatment guidelines as class recommendation, it has been determined that i.v. iron preparations show favorable effects in the prognosis of HF in randomized trials. In patients with ferritin <100 µg and/or Hb 9-12 mg/L, the favorable effect of i.v. iron treatment has been demonstrated. However, results of the trials with erythropoietin stimulating agents in the treatment of anemia in HF are negative. Therefore, their use is not recommended.

CASE-2

Management of drug therapy in patients diagnosed with HF-PEF – Necla Özer

Summary: Approach for drug therapy in a 78-year-old female patient with dyspnea on effort, in NYHA Class II-III, with hypertension (BP 150/95 mm Hg), left ventricular hypertrophy, EF 66%, non-dilated LV, AF (ventricular rate 104/min.), diabetes (HbA1c 7.2%), creatinine 1.4 mg/dL, potassium 4.2 mEq/L, and NT-proBNP 2400 ng/mL.

Case: A 78-year-old female patient presented to the cardiology outpatient clinic with dyspnea on effort which she had for a year; however, it had increased significantly in the last 2 weeks. She had also a chest pain complaint in the form of chest discomfort which increases during exercise in addition to shortness of breath; however, she expressed that she had undergone coronary angiography when she presented with a chest pain complaint 3 months previously and her coronary arteries were found to be normal. Her medical history revealed that she had hypertension (HT), DM and chronic kidney disease (CKD) and received ramipril 5 mg daily, metformin 1000 mg b.i.d. In her physical examination blood pressure (BP) was 150/95 mm Hg and pulse was 98 b.p.m. (irregular) and her functional capacity was in NYHA Class III. Jugular venous distension and first degree pitting edema in the pretibial region were detected. No rales or rhonchi have heard in the lung examination. Although the patient's whole blood count was within normal limits, blood biochemistry values were: HbA1c: 7.2%, potassium: 4.2 mEq/L, serum creatinine: 1.4 mg/dL and NT-proBNP: 2400 ng/L. AF with a ventricular rate of 104 b.p.m. was detected in electrocardiography. Echocardiographic measurements were: left ventricular end-diastolic diameter (LVEDD): 46 mm, LVEF: 66%, septal / posterior wall thicknesses: 12 mm/12 mm, left atrial diameter: 4.3 cm, left atrial volume index: 36.8mL/m^2, left ventricular E/E' ratio: 9.3. Moderate mitral regurgitation and moderate tricuspid regurgitation were detected. There was no left ventricular wall motion abnormality. Systolic pulmonary arterial pressure (sPAP) was measured as 45 mm Hg.

Increase in myocardial wall thickness, enlarged left atrium, increase in E/E' ratio, elevated Nt-proBNP levels and normal LVEF were consistent with HF-pEF manifestation in our patient who presented with long-term hypertension and HF symptoms and signs. Since correcting conditions that are treatable with interventional/surgical methods and effective medical treatments provide significant benefits in the management of these patients, the causes that may lead to diastolic dysfunction, such as CAD, aortic valve diseases, storage/infiltrative myocardial diseases, should be excluded primarily in these types of patients. CAD and severe valve diseases were excluded in our patient. Blood pressure was measured as 150/95 mm Hg. However, it was understood from her history that the patient did not receive any effective medical treatment. One of the most important causes of sudden decompensation in patients with HF-pEF is sudden increases in blood pressure causing an increase in afterload.

In our patient with DM and CKD, the target of blood pressure of <150/90 mm Hg seemed to be acceptable in accordance with the recently published guidelines. However, one of the important problems in this patient was renal dysfunction, which is one of the frequently observed conditions in the group of patients with advanced age. Before investigating the permanent causes of renal dysfunction, the use of both ACEIs or ARBs and hypovolemia, which can be observed commonly in patients in this age group, should be reviewed. Moreover, renal parenchymal injury associated with hypertension or diabetes, secondary hypertension that may develop secondary to renal artery stenosis and renal dysfunction should be considered. Therefore, eliminating renal pathologies is very important with regard to the selection of medical treatment.

Based on this information, it is clear that more effective blood pressure control is mandatory when exclusion of CAD, elimination of secondary HT and DM and renal dysfunction developing secondary to renal dysfunction are considered. Therefore, when ACEI or ARB in combination with thiazide is initiated, the renal functions of the patient should be monitored closely. One of the most important subjects is the monitorization of BP in daily life which was controlled in-hospital setting. Considering that intensive antihypertensive treatment may cause orthostatic hypotension in this group of patients, before being discharged from the hospital, blood pressure must be measured in sitting and standing positions regarding orthostatic hypotension and, if necessary, it should be evaluated with a 24-hour ambulatory BP monitorization depending on the efficacy of the treatment and complaints of the patient.

Since our patient had HF-PEF, it is quite important to try to convert AF to sinus rhythm if possible, and if it is not, to ensure rate control. Digoxin use is not suitable for rate control for AF in these patients. BBs or CCBs may be preferred in rate control. OACs should also be initiated in the patient. One of the important issues concerning our patient was that the typical history of angina persisting although CAD was excluded by the coronary angiography. In this context, third generation BBs or CCBs may be given to the patient in addition to the baseline treatment to help provide efficient BP control and reduce chest pain. Since our patient has AF, it makes sense to select a CCBs from the non-dihydropyridine group (verapamil-diltiazem). Moreover, it should be kept in mind that intensive diuretic therapy particularly in HF-PEF may lead to further impairment in renal functions even if the patients require to receive diuretic treatment in their decompensated period. Accordingly, overadministration of diuretics to these patients in acute decompensation period should be avoided. Further, since spironolactone administration reduces hospitalizations according to the results of the trials conducted with spironolactone, it may be considered as an additional choice.

In the light of all this information, the patient underwent transesophageal echocardiography (TEE) before cardioversion. Thrombus in the left atrial appendix was observed. With these findings, cardioversion was given up. Spironolactone 25 mg and HCTZ 25 mg combination daily, metoprolol succinate 25 mg b.i.d. and warfarin 5 mg o.d were added to the ramipril 5 mg therapy for blood pressure control, AF rate control and congestion control. In her follow-up 5 days later, BP was 145/90 mm Hg, AF rate was 94 b.p.m., creatinine was 1.5 mg, and potassium was 4.9 mEq/L. Metoprolol was increased to 50 mg b.i.d. Verapamil 40 mg t.i.d. was added to the therapy for optimal blood pressure and AF rate control in the follow-up 7 days later. Dose optimization was planned based on the monitoring of blood pressure, AF ventricular rate and renal functions.

CASE-3

Drug therapy management in a systolic HF patient with hyperlipidemia and coronary artery disease – Merih Kutlu

Summary: Additional drug therapy approach in a patient with a diagnosis of HF in NYHA Class II, with EF 32%, NT-proBNP 4300 pg/mL, dilated right and left ventricle, diabetes, diffuse small vessel disease in coronary angiography, not suitable for coronary revascularization, creatinine 1.3 mg/dL, potassium 4.9 mEq/L, LDL-C 184 mg/dL, TG 320 mg/dL, HDL-C 28 mg/dL, AST 62 U/L, ALT 58 U/L who is on ACEI + BB + MRA therapy.

Case: A 63-year-old male patient with the diagnosis of HF, CAD, and DM presented to the hospital with recently increased shortness of breath (NYHA Class II) and decrease in effort capacity. The cardiovascular system examinations were: BP 150/95 mm Hg, heart rate 85 b.p.m., regular rhythm, normal heart and lung sounds. There were no signs of volume overload.

Normal sinus rhythm, R wave loss in precordial leads, nonspecific ST-T changes were detected in ECG. Transthoracic echo revealed right and left ventricular dilation, mild mitral insufficiency with a 32% of EF. The biochemical analysis were: fasting blood glucose 98 mg/dL, hemoglobin 13.4 gr/dl, creatinine 1.3 mg/dL, potassium 4.9 mEq/L, NT-proBNP: 4300 pg/mL, LDL-C 184 mg/dL, TG 320 mg/dL, HDL-C 28 mg/dL, AST 62 U/L, ALT 58 U/L, troponin normal, uric acid: 5.7 mg/dL, HbA1C: 7% and body mass index: 27.

Coronary angiography showed diffuse CAD that was considered to be not suitable for revascularization. Patient was receiving ACEI (ramipril 2.5 mg daily), BB (metoprolol 50 mg daily), MRA (spironolactone 25 mg daily), and metformin (750 mg b.i.d) as an anti-diabetic drug. The patient stated that although his doctor recommended statins and acetylsalicylic acid (ASA 100 mg daily), he stopped taking them and did not comply with life style changes.

In summary, our patient was a HF-REF patient with CAD and diabetes representing a NYHA Class II dyspnea but his medications were not optimal.

The patient has the diagnosis of CAD and DM, however, was not receiving ASA. Therefore, ASA 100 mg o.d was initiated. Also according to ATP IV and ESC guidelines, the patient must have taken statin therapy; however, he did not. The patient whose LDL-C was 184 mg/dL was initiated on a high-dose statin (rosuvastatin 40 mg daily) in addition to the recommendations for life

style changes. Since the ALT and AST values of the patient were lower than 3 times higher the upper limit of normal, this hepatic abnormality was not a contraindication for statin initiation. Fibrate therapy was not considered at this stage because he did not comply with life style changes and did not use statin.

Despite the use of ACEI, BB and MRA therapy, patient has had dyspnea. His medications were appropriate for CAD, HF and DM. However, despite this treatment, BP was still mildly elevated, his resting heart rate was >70 b.p.m. and he was in NYHA functional class II.

In such a patient with DM, target BP should be <140/90 mm Hg according to JNC 8 and ASH/ISH 2014 guidelines and <140/85 mm Hg according to the ESC Hypertension Guidelines. In terms of HF, the target heart rate is <70 b.p.m. in patients with sinus rhythm. Ramipril dose was increased to 5 mg daily and metoprolol dose to 100 mg daily for the goals of BP control, reducing heart rate to <70 b.p.m. and up-titrating the HF medications. The dose of MRA 25 mg daily was not changed.

The patient has a BMI of 27 and was educated in detail about the drugs he has been receiving, newly recommended drugs and lifestyle changes (such as daily drug intake, BP monitoring, heart rate monitoring, diet, salt restriction, exercise, weight loss). It was emphasized strongly that he should not discontinue statin and ASA therapy. Loop diuretics were not considered since there was no volume load. BB dose was primarily increased to reduce heart rate. The patient was given a BP chart and a 10 day follow-up was scheduled.

At 10-day follow-up visit, BP was found to be 135/85 mm Hg, heart rate was 66 b.p.m. with regular rhythm, creatinine was 1.3 mg/dL and potassium was 5.1 mEq/L. Patient was recommended to continue the current therapy and a one-month follow-up visit was scheduled. Considering the drugs recently initiated and that the doses of which were increased, a plan was made to evaluate the fasting lipid profile, ALT, AST, creatinine and potassium levels.

CASE-4

Management of HF therapy in a patient presenting with low cardiac output, borderline hypotension and hyponatremia – Mahmut Şahin

Summary: Drug therapy approach in a patient with HF; NYHA III, BP 95/70 mm Hg, heart rate 89 b.p.m. in sinus rhythm, EF 16%, peripheral +++ edema, NT-proBNP 8600 pg/mL, creatinine 1.4 mg/dL, sodium 124 mEq/L, potassium 4.7 mEq/L.

Case: A case of 73-year-old female patient was admitted to the hospital with a gradually increasing shortness of breath for the last two weeks. The functional capacity was evaluated as NYHA Class III. In physical examination, the blood pressure was 95/70 mm Hg and the heart rate was 89 b.p.m. in sinus rhythm. Crepitant rales at the basal segments of the lungs and pretibial +++ edema were detected. Her medical history revealed that she underwent coronary angiography 7 years ago, had normal coronary arteries and a CRT-D device had been implanted for cardiac resynchronization 3 years ago. The patient was on carvedilol 6.25 mg b.i.d., ramipril 2.5 mg daily, furosemide 40 mg daily and digoxin 0.125 mg daily. EF was measured to be 16% and severe global hypokinesia was detected by transthoracic echocardiography. The laboratory findings were: sodium 124 mEq/L, creatinine 1.4 mg/dL, potassium 4.7 mEq/L, NT-proBNP: 8600 pg/mL. The patient was admitted to the cardiology department with the diagnosis of decompensated HF.

Worsening in her symptoms was considered to be due to congestion. Borderline hypotensive systolic blood pressure was considered as the sign of low cardiac output. Low sodium values were related to hypervolemic hyponatremia manifestation. Fluid intake was restricted to 0.5-1 L per day for the treatment of hyponatremia and congestive symptoms. Daily weight and urine output monitorization was performed. IV furosemide 40 mg b.i.d. was given as a diuretic therapy. Since her systolic blood pressure was <100 mm Hg, IV vasodilator therapy for hemodynamic congestion could not have been applied. Her medical treatment with carvedilol, ramipril and digoxin was continued. Serum digoxin level was measured as 0.9 ng/mL.

Expected increase in diuresis and improvement in hyponatremia were not achieved despite diuretic therapy within the 48-hours follow-up. IV furosemide infusion 10 mg per hour was initiated and dopamine infusion at a renal vasodilator dose of 2 µgr/kg/min was added to increase urinary output. However, improvements in diuresis and hyponatremia were not achieved. Diuretic dose was not further increased due to the risk of both worsening renal functions and reducing blood pressure. Tolvaptan 15 mg daily was added to the therapy. Diuretic dose was reduced to half dose. Sodium was monitored for 8 hours in the first day. Following initiation of tolvaptan therapy, urinary output increased without worsening BP and creatinine levels. Invasive monitorization was not considered as it was believed to provide no further benefit since the clinical signs and monitorization of the patient were optimal. Sodium level increased to 133 mEq/L in the 5th day. Pretibial edema regressed significantly. Tolvaptan was discontinued upon detection of 10% reduction in body weight and relief of symptoms. Diuretic therapy continued orally. Spironolactone 25 mg daily was added to the current therapy. Since she could barely tolerate carvedilol 6.25 mg b.i.d. therapy and her BP did not allow beta blocker up-titration, she was discharged from hospital upon planning to initiate ivabradine treatment according to the level of heart rate at 7-day of her follow-up.

28.0 Appendix – Hakan Altay

28.1 Angiotensin-converting enzyme inhibitors/ Angiotensin receptor blockers

Treatment indications

Should be used in all HF patients with EF <40%.

First line treatment in New York Heart Association (NYHA) Class II-IV patients; treatment should be initiated as soon as possible.

Also beneficial in asymptomatic patients with left ventricular systolic dysfunction (NYHA Class I).

Should be used in all patients who develop left ventricular systolic dysfunction after MI.

ARBs can be used in patients who cannot tolerate ACEIs.

Starting and target doses

Should be started with the lowest dose and increased to the target or tolerated dose.

Double the dose at not less than 2-week intervals.

Starting and target doses of ACEIs/ARBs are shown in Table 42 and Table 43.

Contraindications

History of angioedema

Known bilateral renal artery stenosis

Pregnancy/risk of pregnancy

Conditions which require dose reduction or discontinuation

When significant hyperkalemia (Serum K >5 meq/L) develops, first of all potassium-sparing diuretics should be discontinued. If it continues, ACEI/ARB dose should be reduced.

When severe hyperkalemia develops (Serum K >5.5 meq/L), ACEIs/ARBs should be stopped.

ACEIs/ARBs may continue to be used until an increase in creatinine (Cr) of up to 50% above baseline or Cr of 3 mg/dL.

If greater rise in creatinine persists, other nephrotoxic drugs should be discontinued first and if there is no congestion, the diuretic dose should be decreased.

When there is an increase in creatinine in the range of 50-100%, the ACEI/ARB dose should be halved and renal functions should be rechecked within 1-2 weeks.

If creatinine increases by >100% or to >3.5 mg/dL or GFR <20 mL/min/1.73 m^2, ACEI/ARB should be stopped.

In case of hypotension, before discontinuing ACEI/ARB dose diuretic dose should be optimized and other antihypertensives should be discontinued first and then ACEI/ARB dose should be reduced.

If there is symptomatic or severe asymptomatic hypotension (systolic blood pressure <90 mm Hg) despite above mentioned precautions, ACEIs/ARBs should be stopped.

28.2 Beta-blockers

Treatment indications

Potentially all symptomatic patients with stable systolic HF (EF <40%).

Table 42. Starting and target doses of drugs recommended in the ESC HF 2012 guidelines (3)

Drug	Starting dose	Target dose
Angiotensin converting enzyme inhibitors		
Captopril, mg, t.i.d.	6.25	50-100
Enalapril, mg, b.i.d.	2.5	10-20
Lisinopril, mg, o.d.	2.5-5	20-35
Ramipril, mg, o.d.	2.5	5
Trandolapril, mg, o.d.	0.5	4
Perindopril, mg, o.d.	2.5	10
Angiotensin receptor blockers		
Candesartan, mg, o.d.	4-8	32
Valsartan, mg, b.i.d.	40	160
Losartan, mg, o.d.	50	150
Beta-blockers		
Bisoprolol, mg, o.d.	1.25	10
Carvedilol, mg, b.i.d.	3.125	25-50
Metoprolol succinate, mg, o.d.	12.5-25	200
Nebivolol, mg, o.d.	1.25	10
Mineralocorticoid receptor antagonists		
Spironolactone, mg, o.d.	25	25-50
Eplerenone, mg, o.d.	25	50
Loop diuretics		
Furosemide, mg	20-40	240
Bumetanide, mg	0.5-1	5
Torasemide, mg	5-10	20
Ivabradine		
Ivabradine, mg, b.i.d.	5	7.5
Digoxin		
Digoxin, mg, o.d.	0.125-0.25	0.25
Hydralazine – isosorbide dinitrate (H-ISDN)		
H-ISDN, mg, t.i.d.	37.5/20	75/40

All patients who developed left ventricular systolic dysfunction after MI.

First-line treatment (along with ACEIs/ARBs and MRAs) in stable HF patients; start as early as possible in the course of disease.

Starting and target doses

Should be started with the lowest dose and tried to increase to the target or maximum tolerated dose.

Double the dose at not less than 2-week intervals; slower uptitration may be needed in some patients.

Starting and target doses of BBs are shown in Table 42 and Table 43.

Contraindications

Asthma (COPD is not a contraindication)

Table 43. Starting and target doses of drugs recommended in the ACC/AHA HF 2013 guidelines (4)

Drug	Starting dose	Target dose
Angiotensin converting enzyme inhibitors		
Captopril, mg, t.i.d.	6.25	50
Enalapril, mg, b.i.d.	2.5	10-20
Fosinopril, mg/g	5-10	40
Lisinopril, mg/g	2.5-5	20-40
Perindopril, mg/g	2	8-16
Quinapril, mg, b.i.d.	5	20
Ramipril, mg/g	1.25-2.5	10
Trandolapril, mg/g	1	4
Angiotensin receptor blockers		
Candesartan, mg/g	4-8	32
Losartan, mg/g	25-50	50-150
Valsartan, mg, b.i.d.	20-40	160
Beta-blockers		
Bisoprolol, mg/g	1.25	10
Carvedilol, mg, b.i.d.	3.125	50
Carvedilol CR, mg/g	10	80
Metoprolol succinate, mg/g	12.5-25	200
Aldosterone antagonists		
Spironolactone, mg/g	12.5-25	25 (or b.i.d.)
Eplerenone, mg/g	25	50
Hydralazine – isosorbide dinitrate (H-ISDN)		
Fixed dose combination, mg	37.5 hydralazine + 20 ISDN t.i.d.	75 hydralazine + 40 ISDN t.i.d.
Hydralazine + Isosorbide dinitrate	25-50 mg, t.i.d./q.i.d. + 20 – 30 mg, t.i.d./q.i.d.	300 mg/g (in divided doses) + 120 mg/g, (in divided doses)

2nd or 3rd degree atrioventricular block (not contraindicated in the presence of a pacemaker)

Conditions which require dose reduction or discontinuation

Severe (NYHA Class IV) HF (should be continued as long as possible).

Worsening HF currently or recently (<4 weeks) (should be continued as long as possible).

Worsening heart block or symptomatic bradycardia (<50/min)

Hypotension (systolic blood pressure <90 mm Hg) or low output signs.

28.3 Mineralocorticoid receptor antagonists

Treatment indications

Potantially all patients with persisting symptoms (NYHA Class II-IV) and an EF <35% despite treatment with ACEIs (or ARBs) or BBs.

Patients with symptomatic HF or DM who develop systolic dysfunction (EF <40%) after MI.

Starting and target doses

Should be started with the lowest dose and tried to increase to the target or maximum tolerated dose.

The dose should be increased every 4-8 weeks.

Potassium, creatinine and GFR are recommended to be checked at 1 and 4 weeks after starting or increasing dose and subsequently at 2, 3, 6, 9, 12 months ; 4-monthly thereafter.

Starting and target doses of MRAs are shown in Table 42 and Table 43.

Contraindications

Serum creatinine level >2.5 mg/dL in males and >2 mg/dL in females.

Concurrent with ACEI and ARB combination.

Concurrent with potassium-sparing diuretics.

Concurrent with potassium supplement.

Conditions which require dose reduction or discontinuation

The dose should be halved if serum K rises above >5.5 mEq/ or creatinine rises to >2.5 mg/dL, and GFR is reduced to <30 mL/min.

It should be stopped if serum K rises to > 6mEq/L or creatinine to >3.5 mg/dL or GFR is reduced to <20 mL/min.

28.4 Diuretics

Treatment indications

All HF patients with symptoms and signs of congestion independent of EF should receive diuretics; diuretics should always be used concurrently with ACEIs (or ARBs), BBs and MRAs in patients with low EF.

Diuretic choice, dose and administration

Generally loop diuretics are used; furosemide is the most commonly used agent.

If diuretic resistance occurs, it can be switched to other loop diuretics (bumetanide or torasemide) or thiazide-type diuretic can be added.

Started with a low dose and dose is reduced according to the patient's congestion status, blood pressure and renal functions.

The lowest possible dose that will maintain euvolemia (dry weight of the patient) should be used.

In the presence of severe congestion, high dose furosemide (oral dose x 2.5) can be administered intravenously or in bolus or infusion forms in the hospital setting.

Starting and maximum doses of diuretics are shown in Table 42 and 43.

Cautions during diuretic therapy

Severe hypokalemia (potassium <3.5 meq/L) may develop

Renal functions may worsen

Severe hyponatremia (<125 meq/L) may develop when used with thiazide diuretics

Symptomatic and asymptomatic hypotension (systolic blood pressure <90 mm Hg) may develop

28.5 Ivabradine, digoxin, hydralazine and/or nitrates treatment

Ivabradine

Treatment indications

Can be used in symptomatic (NYHA Class II-IV) patients in sinus rhythm with systolic HF (EF <35%) and a heart rate >70/min despite treatment with ACEI, BB and MRA therapy

Can be used in symptomatic (NYHA Class II-IV) patients in sinus rhythm with systolic HF (EF <35%) and a heart rate >70/min who cannot tolerate BB therapy.

Starting and target doses

Starting and target doses of ivabradine are shown in Table 42.

Side effects to consider in ivabradine use

Symptomatic bradycardia

Visual defect (Phosphene)

Digoxin

Treatment indications

Can be used in patients with systolic HF (EF <45%) and AF when rate control cannot be achieved with BBs.

Can be used in patients with systolic HF (EF <45%) in sinus rhythm when symptoms persist despite optimal medical treatment with ACEIs/ARBs, BBs and MRAs.

Starting and maintenance doses

There is no need for digoxin loading dose in patients whose clinical condition is stable.

Starting and maintenance doses of digoxin are shown in Table 42.

Conditions/side effects to consider in digoxin use

The dose should be reduced in patients with advanced age, renal dysfunction and low muscle mass.

Drugs such as amiodarone, verapamil, diltiazem, and quinidine may increase digoxin serum level.

Digoxin may cause arrhythmia and heart block particularly in the presence of hypokalemia.

Loss of appetite, nausea, and visual impairment should suggest digoxin intoxication.

Ventricular arrhythmia and advanced AV block may be observed in digoxin intoxication.

Hydralazine and/or nitrates

Treatment indications

Hydralazine/isosorbide dinitrate may be considered as an alternative to an ACEIs/ARB if neither is tolerated in systolic HF (EF <45%) (In addition to BBs or MRAs).

If symptoms persist in patients with systolic HF (EF <45%) despite ACEI (or ARB), beta-blocker and MRA therapy, H-ISDN can be added.

Starting and target doses

Starting and target doses of H-ISDN are shown in Table 42 and Table 43.

Can be started with the lowest dose and increased to the target or maximum tolerated dose by increasing dose every 2-4 weeks.

Side effects to consider in hydralazine/isosorbideuse

May cause headache, hypotension, arthralgia, lupus-like syndromes.

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