Optimal medical treatment for heart failure with reduced ejection fraction

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OPTIMAL MEDICAL TREATMENT FOR HEART FAILURE WITH REDUCED EJECTION FRACTION

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Abbreviations

HF- Heart Failure

EF- Ejection Fraction

LV- Left ventricular

HFrEF- Heart failure with reduced ejection fraction

HFpEF- Heart failure with preserved ejection fraction

HFmrEF- Heart failure with mid-range ejection fraction

LVSD- Left Ventricular systolic Dysfunction

ESC- European Society of Cardiology

ACEI- Angiotensin-converting enzyme inhibitor

ARB- Angiotensin receptor blocker

MRA- Mineralocorticoid receptor antagonist

ARNI- Angiotensin receptor-Neprilysin inhibitor

CCB- Calcium-channel blocker

JVP- Jugular venous pressure

MI- Myocardial infarction

HR- Heart rate

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Abstract

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This study assessed the optimal medical therapy for HFrEF among patients in the outpatient clinic of University Hospital Centre Zagreb during the last year and compared the results with a study done by the Croatian HF registry in 2011. I measured improvements in the therapy and compared the results with similar studies performed in the UK.

Patients attending outpatient clinic on Wednesdays at Clinical Hospital Centre Zagreb for the past year were audited. The data collected included clinical features of HF, medications and the doses of medication prescribed which were then compared with the current ESC guidelines. In total, 108 patients were included in the study. Of which, 83 were men (76%) and 25 women (24%). Predominant HF etiology included, dilated cardiomyopathy (49%), ischemic cardiomyopathy (33%) and hypertensive cardiomyopathy (5%). All patients had reduced left ventricular EF and were on HF medication. Ninety-five percent of the patients received beta-blockers (compared with 58% in 2011), 53% were on an ACEI or an ARB (compared with 60% in 2011), 87% received a MRA (compared with 44% in 2011) and 89% were on diuretics (compared with 86% in 2011). Digoxin was given to only 7.5% (compared with 30% in 2011) and ivabradine was used by 3 patients (2.8%). Although this study demonstrated that there is an increase in prescribed doses of HF optimal medication, the mean daily dose of most medical therapy is still significantly below the maximum tolerated evidence-based doses as recommended by the ESC guidelines of 2016.

Keywords: Heart failure with reduced ejection fraction, left ventricular systolic dysfunction, heart failure management, ACE inhibitor, mineralocorticoid receptor antagonist, beta-blocker, angiotensin receptor-neprilysin inhibitor.

Sažetak

OPTIMALNA MEDIKAMENTNA TERAPIJA U BOLESNIKA S REDUCIRANOM SISTOLICKOM FUNKČIJOM.

Autor : Mohammad Tareq Rahimy

U ovom diplomskom radu ispitao sam učestalost propisivanja optimalne medikamentne terapije u bolesnika s popuštanjem srca s reduciranom istisnom frakcijom (HFrEF, engl. heart failure with reduced ejection fraction) i usporedio dobivene rezultate sa izvješćem Hrvatskog registra bolesnika sa zatajivanjem srca iz 2011. godine. Mjerio sam poboljšanja u terapiji i usporedio dobivene rezultate sa sličnim studijama provedenim u Velikoj Britaniji.

U ispitivanje su uključeni bolesnici koji su posjetili Ambulantu za zatajivanje srca srijedom u Kliničkom bolničkom centru Zagreb tijekom protekle godine. Prikupljeni podaci uključili su kliničke značajke HFrEF-a, vrste i propisane doze lijekova koji su zatim uspoređeni s važećim smjernicama Europskog kardiološkog društva. Ukupno je uključeno 108 bolesnika, od čega 83 muškarca (76%) i 25 žena (24%). Glavni uzroci HFrEF-a bili su dilatacijska kardiomiopatija (49%), ishemijska kardiomiopatija (33%) i hipertenzivna kardiomiopatija (5%). Svi bolesnici imali su disfunkciju LV s reduciranom EF i liječeni su lijekovima za srčano popuštanje. Devedeset pet posto bolesnika primalo je beta-blokatore (u usporedbi s 58% u 2011.), 53% je uzimalo ACEI ili ARB (u usporedbi s 60% u 2011.), 87% je liječeno MRA (u usporedbi s 44% u 2011.) i 89% je bilo na diureticima (u usporedbi s 86% u 2011). Digoksin je propisan samo u 7,5% (u usporedbi s 30% u 2011.), dok je ivabradin propisan samo u 2,8%.

Ovo istraživanje je pokazalo da usprkos porastu učestalosti propisivanja lijekova za optimalno liječenje bolesnika s HFrEF, srednja dnevna doza lijekova u većine bolesnika i dalje je znatno ispod maksimalnih doza kakve su preporučene u posljednjim Smjernicama ESC za liječenje bolesnika sa zatajivanjem srca iz 2016. godine.

Ključne riječi: Optimalno liječenje bolesnika s HFrEF, disfunkciju LV s reduciranom EF, ACEI, ARB.

Introduction

Heart failure is complex and common clinical syndrome that can result from any structural and functional cardiac impairment in which either the ability of ventricular filling or ejection of blood form the ventricle is compromised. HF may be caused by an array of different disorders of the myocardium, pericardium, endocardium, heart valves and vessels and certain metabolic disorders. Most HF patients however, have symptoms due to left ventricle myocardial dysfunction. LV dysfunction is categorized into HF with reduced ejection fraction (HFrEF) diagnosed when LVEF <40 % (also known as systolic HF), and HF with preserved ejection fraction (HFpEF) typically considered as LVEF≥50 % (known as diastolic HF). In the last ESC guidelines from 2016 a new term was introduced which covers patients with HF with a LVEF that ranges from 40% to 49% termed as heart failure with mid-range ejection fraction (HFmrEF).

Dyspnea, fatigue and fluid retention are the most typical manifestation of a patient presenting with HF that may be accompanied by signs such as elevated JVP and pulmonary crackles. Dyspnea and fatigue may limit exercise tolerance, whereas fluid retention may lead to pulmonary and/or splanchnic congestion and peripheral edema. After the diagnosis, it is central to demonstrate an underlying cardiac cause of HF such as abnormalities in the myocardium. This is crucial for therapeutic reasons, as the exact pathology determines the choice of treatment used (1)(2).

HF Terminology

The current definition and terminology used in patients with HF is restricted to phases at which clinical symptoms become apparent. However, before any clinical symptoms become apparent, asymptomatic patients already have structural and functional systolic or diastolic LV abnormalities, which are precursors to symptomatic HF with poor outcomes. It is therefore important to note that recognizing patients at the asymptomatic precursor stage may reduce mortality(1).

Historically HF has been classified based on the location of the failure such as left ventricular, right ventricular or biventricular or based on time of onset e.g. acute or chronic HF. Clinically, the main terminology used to describe HF is based on LVEF usually measured using echocardiography. Normal LVEF is typically considered to be greater than ≥50% also known as HF with preserved EF (HFpEF). Patients with reduced LVEF are those with <40% (HFrEF). LVEF in the range of 40-49% is now defined as mid-range or HFmrEF. It is important to differentiate patient with HF based on LVEF as it will narrow down the etiology, demographics, comorbidities and response to therapy (3)

Epidemiology and etiology of HF

The prevalence of HF is relatively high, though it depends of the definition applied. In the developed countries it is estimated that approximately 1-2% of the adult population suffer from symptoms of HF. This number is known to rise to ≥10% among people >70 years of age (4). According to the Rotterdam study from 2004, the lifetime risk of HF at age 55 years is estimated to be 33% for men and 28% for women (5).

The epidemiological and etiological profiles between HFpEF and HFrEF are shown to be different. Patients with HFpEF are usually older women and more commonly have a history of high blood pressure and atrial fibrillation (AF), while myocardial infarction (MI) most commonly precede HFrEF. The features of patients with HFmrEF are not yet clearly known and therefore future studies should aim to characterize these populations (6).

Concerning the etiology of HF; these vary among world regions. Additionally there is much overlap between several pathologies whether it may be cardiovascular or non cardiovascular that connive to cause HF. Consequently to this, there is no agreed single classification for the cause of HF (2). Thus, the diagnostic work up should include identifying these diverse pathologies to apply the best possible therapeutic intervention.

The etiologies of HF could be due a diseased myocardium such as ischemic heart disease, toxic damage, infiltration, metabolic derangements and genetic

abnormalities. Ischemic heart disease and genetic abnormalities in HCM, DCM and restrictive cardiomyopathy may be more commonly seen.

Another cause of HF may be due to abnormal loading. Conditions such as hypertension, valve and myocardium structural defects, high output states, volume overload. Pericardial and endomyocardial pathologies are also known etiologies of HF. Furthermore; tachyarrhythmias are also associated with HF (4)(5)(6).

Pharmacological treatment of Heart failure

Evidence-based medicine suggests that onset of symptomatic HF may be delayed or even prevented if timely interventions are carried out to treat asymptomatic LV systolic dysfunction and controlling other modifying risk factors. Many clinical trials have shown that controlling hypertension will delay onset of HF and may even prolong life (7)(8)(9). Therefore many antihypertensive medications have shown to be very effective in treating HF both in patients with and without a history of MI (7)(8)

The goal of pharmacological intervention in HF is to improve patient's quality of life by preventing hospitalization, improve functional capacity and clinical status and ultimately to reduce mortality.

Guideline-directed medical therapy for HFrEF includes four drug classes that reduce mortality. Angiotensin-converting enzyme inhibitor (ACEI), angiotensin-receptor blockers (ARB), mineralocorticoid receptor antagonist (MRA) and beta-blockers have all shown to improve survival in patients with HFrEF and are recommended for use in all these patients unless contradicted or not tolerated. But even with maximal therapy with these drugs, symptoms may persist and mortality remains high(2).

A novel drug therapy known as LCZ696 has been found to lower mortality in theses patients. Angiotensin Receptor Neprilysin Inhibition (ARNI) versus ACEI (enalapril) was investigated in the recently completed PARADIGM-HF trial (10). Treatment with LCZ696 for a median of 27 months resulted in relative reduction of 20% in death from cardiovascular causes and hospitalization. The trial also showed an

overall mortality reduction of 16% compared to enalapril(11). This compound that combines an ARB (valsartan) and a neprilysin inhibitor (sacubitril) is therefore recommended by the ESC-guidelines to replace ACEIs in HFrEF patients who are still symptomatic despite optimal pharmacological treatment.

A symptomatic HFrEF patient should initially be put on a combination of ACEI and a Beta-Blocker and followed up. If the patients remain symptomatic, MRA should be added and titrated up to maximum tolerated evidence-based dose. Upon review if still symptomatic with LVEF<35%, ACEI should be replaced with angiotensin receptor neprilysin inhibitor (ARNI) in patients who are able to tolerate ACEI and/or ARB(2).

MRAs are drugs that block receptors that bind aldosterone and other steroid hormones. ESC guidelines recommend the use of spironolactone or eplerenone in all symptomatic patients with HFrEF and LVEF of 35% or less in spite of treatment with ACEI and a beta-Blocker, which is associated with a reduction in mortality from cardiovascular causes or hospitalization from HF (2)(12)(13). MRAs should be used cautiously in patients with impaired renal function and in those with serum potassium levels >5.0 mmol/L. Therefore, regular renal function tests and serum potassium levels should be performed in regular intervals according to local clinical guidelines.

Guidelines also recommend the use of ivabradine, which is shown to improve outcome by reducing elevated heart rate, which is often seen in HFrEF. Ivabradine inhibits the *If* channel in the sinus node and should therefore only be used for patients with sinus rhythm. The European Medicine Agency (EMA) approved ivabradin for use in patients with HFrEF in sinus rhythm with a resting HR of 75 bpm or above. In this group of patients ivabradine showed a survival benefit according to SHIFT study analysis performed in 2013 by Bohm M et al. (14) However, if the patient has sinus rhythm with QRS duration of > 130 msec then the need for CRT should be evaluated (14).

If after careful use of the above-mentioned optimal therapy, the patient still has resistant symptoms, then the use of left ventricular assist device (LVAD) or heart transplantation should be considered (2).

Diuretics should be used in conjunction with above-mentioned medications in patients with signs of congestion (2). Even though the effects of diuretics on mortality and morbidity is not fully investigated, a Cochrane meta-analysis from 2012 conducted by Faris R et al. (15) concluded that conventional diuretics have shown to reduce the risk of death and worsening of HF compared with placebo. Furthermore, it also appeared to improve exercise tolerability compared to active control.

An important point that needs mentioning is that the recommended drugs should be up titrated to the maximum tolerated evidence-based dose to achieve full therapeutic effects. A good example of which is ACEIs. In a study of Pan-European registry from 2013, Maggioni AP et al. (12) reported that majority of HF patients receive suboptimal doses of ACEI and thus suggested that the current guidelines regarding dosages of HF medication should be seriously considered in daily clinical practice.

Furthermore, it is also important to mention drugs that are not recommended and believed to cause harm in symptomatic patients with HFrEF. These drugs consist of calcium-channel blockers (CCBs). Non-dihydropyridine CCB such as diltiazem was shown to cause more cardiac events in patients with left ventricular dysfunction compared to the placebo group in The Multicentar Diltiazem Postinfarction Trial (MDPIT) (16). Among the dihydropyridine CCBs, only amlodipine and felodipine have shown to have positive safety profiles in patients with HFrEF, but should only be used if there is considerable indication for use for such drugs in patients with HF (17)(18).

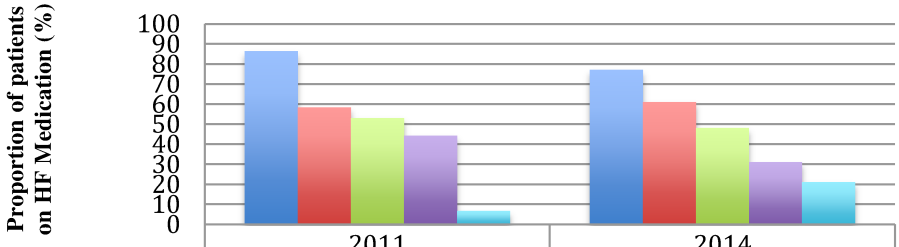
HF in Croatia

According to the European statistical website "Eurostat" Cardiovascular diseases are the leading cause of morbidity and mortality in Croatia, with a mortality rate of 48.3% in 2012 trending down to 48.1% in 2013.

The Croatian Registry of HF has been collecting data on patients with HF since October 2005 and in 2011 they published an article emphasizing the etiology and treatment of HF across hospitals in Croatia while comparing it with the European guidelines with the intention to improve the treatment modalities and thus survival rate of HF.

In this study 1,868 patients treated for HF since the start of the registry were included and analyzed. Of these, there were 1,243 patients who had established chronic HF. The authors also analyzed the leading predisposing factors for HF in these patients to be in the first place: arterial hypertension (50.8%), followed by atrial fibrillation (46.1%) and then infection (15.1%).

According to the data from the Registry, the most prescribed drug upon discharge were diuretics (86.3% in 2011 vs. 77 in 2014) followed by beta-blockers (58.3% in 2011 vs. 61% in 2014), ACEI (53% in 2011 vs. 48% in 2014), MRAs (44.2% in 2011 vs. 31% in 2014) and ARBs (6.6% in 2011 vs. 21% in 2014).



	2011	2014
Diuretic	86.3	77
Beta-Blockers	58.3	61
ACEIs	53	48
MRAs	44.2	31
ARBS	6.6	21

Fig 1. Proportion of patients on HF medication in 2011 and 2014.

According to the data above, the proportion of patients receiving optimal medical therapy in 2014 decreased for diuretics and MRAs. The use of beta-blockers increased slightly in comparison with 2011 but the use of ARBs increased by almost 3-fold, while the use of ACEI remained stable (19)(20).

Daily doses for ACEI prescribed in 2011 were: lisinopril (9 mg), ramipril (3.5 mg), trandolapril (1.8 mg), fosinopril (9 mg), cilazapril (3 mg), enalapril (6.8 mg), perindopril (3.4 mg) and captopril (100 mg). Mean daily dose of beta-blockers was calculated to be 2.8 mg for bisoprolol and 26.1 mg for carvedilol (19).

Table 1. Mean daily dose of HF medication in 2011 versus recommended target dose.

	Mean Daily Dose Given in 2011 (mg)	Recommended Target Dose according to ESC guideline (mg)
ACE-I		
Captopril	100	150
Enalapril	6.8	20-40
Lisinopril	9	20-35
Ramipril	3.5	10
Trandolapril	1.8	4
Beta-Blockers		
Bisoprolol	2.8	10
Carvedilol	26.1	50
Nebivolol		10

Both ACEI and beta-blockers mean daily doses given in 2011 were significantly below the maximum tolerated evidence-based doses to achieve maximal therapeutic effect. We hope to see an improvement on this data in this study.

HF in the UK

HF in the UK accounts not only as a major economic burden but also major burden on the NHS where it accounts for 1 million inpatients bed days which is equivalent to 2% of the NHS total. Notably, this number can only further increase, due to the aging population. Both national and international guidelines are suggested to be used in the treatment of HF as they summaries based on evidence, most current recommendations on treatment of HF. In the UK the National Institute for Health and Care Excellence (NICE) highlights key priorities that need to be implemented for the treatment of HF(20)(21).

In two different audit cycles performed in 2010-2011 and 2013-2014, all HF patients with reduced EF who attended Royal Brompton Hospital were included in the study and reviewed for optimal medical treatment, maximum tolerated doses and education of the patients regarding the benefits of exercise in chronic HF.

In both cohort from 2011 and 2014, main four HF drug classes were used according to both NICE and ESC guidelines, however the authors did notice a significant increase in the proportion of patients being prescribed the maximum tolerated dose. The proportion of patients receiving maximum daily dose of beta-blocker increased from 77% in 2011 to 89% in 2014, ACEI/ARB from 86% in 2011 to 91% in 2014 and MRA increased from 44% in 2011 to 56% in 2014(22).

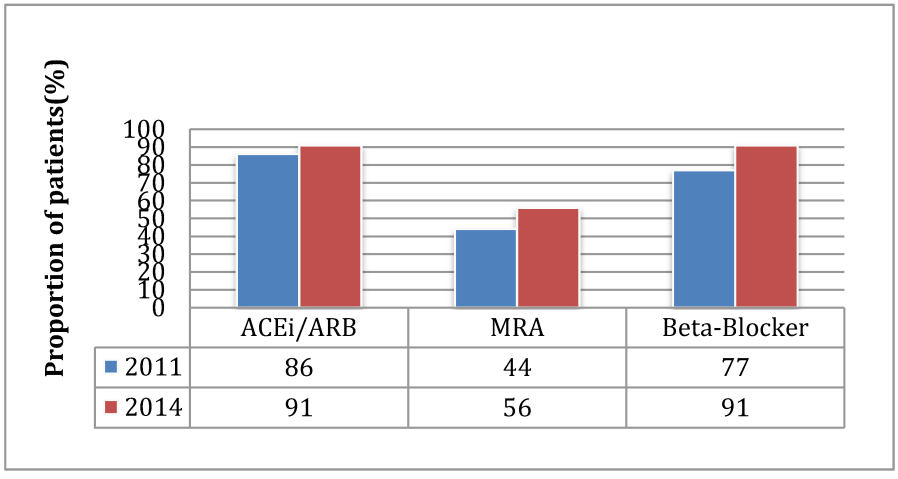


Fig 2. Proportion of patients on HF medication in the UK in 2011 and 2014.

The comparison of two audits show that the rate of compliance of the physicians to adhere to both national and international guidelines when treating chronic HF generally increased from 2011 to 2014. Not only, there was an improvement seen on the rates of prescription for evidence-based pharmacotherapies but also clear improvement in prescribing maximum tolerated dose and monitoring of HF patients (23).

Another point of priority in this audit was education of HF patients about exercise and cardiac rehabilitation. The authors noted that although the number of patients who were educated about the benefits of regular exercise increased from 36% in 2011 to 100% in 2014, the actual number of patients that were referred to a HF rehab program or enrolled in HF rehab program still remained very low. The reason behind could be due to inadequate levels of patient participation either due to financial restrictions or lack of rehabilitation services geographically within reach and for the comorbid and elderly patient, lack of home-based alternative (23).

Aim of the Study

The primary objective of this pilot study was to see:

1) If the ESC guideline regarding the optimal medical therapy of HFrEF is being adhered in daily clinical practice and to what percentage are they adhered to?

2) To compare the results with the results published in 2011 (18) by Croatian HF registry and one in 2014 by Croatian Cardiac Society regarding treatment of HF in Croatia (19) and to observe the changes and improvements.

3) To compare the result with similar study performed in the UK and to contrast the use of optimal medical therapy in HFrEF between Croatia and the UK.

Methods

In this retrospective study, the data was collected from the Electronic Data Base at the University Hospital Center Zagreb. The study population included patients who visited the HF outpatient clinic. I obtained the data from only the patients who visited the clinic on a Wednesday and had EF< 40%. Furthermore, full medical treatment they were receiving and the clinical feature of HF were noted which I then used to conclude and discuss my results.

Results

In total, 108 chronic HF patients were included in the study that was all treated in the outpatient clinic in the period of 2017-2018 at the University Hospital Centre Zagreb. Of these, there were 83 men (76.8% with an average age of 61 years), and 25 women (23.2% with an average age of 62 years).

Etiology

The predominant etiology of HF was dilated cardiomyopathy (49%) and ischemic cardiomyopathy (37%) and hypertensive cardiomyopathy (5%). Other etiologies that together comprised 9% of the total include: tachy-cardiomyopathy, valvular cardiomyopathy and toxic cardiomyopathy.

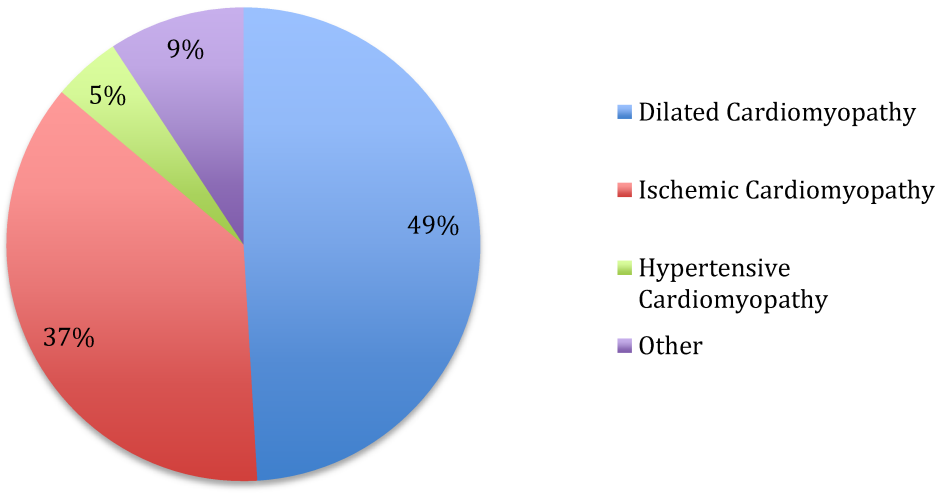


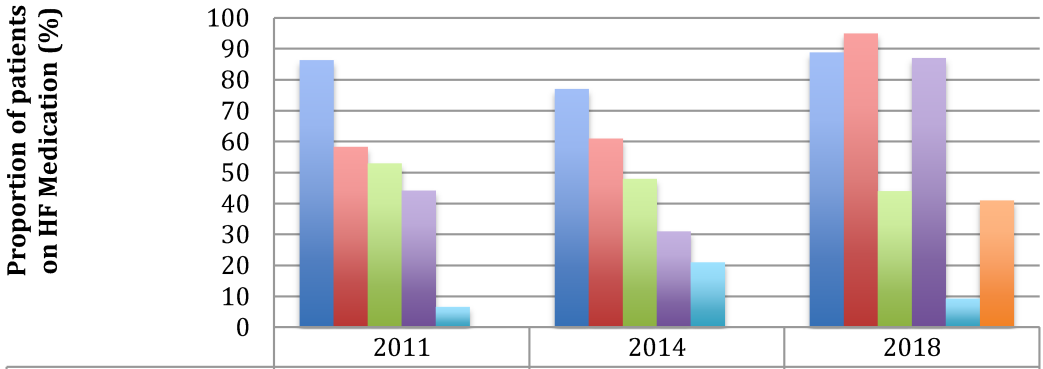
Fig 3. Predominant etiology of HF

Diagnosis

All the patients included in the study have HF with reduced EF that was studied either by an echocardiogram or magnetic resonance. However only 62 of them (57%) were ordered to do a blood test for plasma NTproBNP marker.

Treatment on Discharge for HF

Fig 4. Proportion of patients on HF medication



	2011	2014	2018
Diuretic	86.3	77	88.8
Beta-Blockers	58.3	61	95
ACEIs	53	48	44
MRAs	44.2	31	87
ARBS	6.6	21	9.3
Sacubitril/Valsartan	0	0	41

Table 2. Table comparing mean daily dose of HF medication in 2018 with 2011 and recommended target dose according to ESC guidelines.

	Mean Daily Dose Given 2011(mg)	Mean Daily Dose Given 2018 (mg)	Recommended Target Dose according to ESC guidelines (mg)
ACE-I			
Ramipril	3.5	4	10
ARBs			
Valsartan	-	158	320
Beta-Blockers			
Bisoprolol	2.8	5.2	10
Carvedilol	26.1	32	50
Nebivolol	-	5.8	10
ARNI			
Sacubitril/Valsartan	-	236.4	400
MRA			
Spironolactone/ Eplerenone	-	34.2	50
Diuretics			
Furosemid	-	93	40-240

ACEI and ARB

Forty-four percent of patients were discharged on an ACEI, and 53% of the patients received either and ACEI or an ARB on discharge. There is a slight decrease in number of patients receiving ACEIs compared with the data from the Croatian HF registry from 2011 and 2014 (20). This may be due to introduction of the new combination drug - sacubitril/valsartan. The mean daily dose on discharge was 4.2 mg for ACEIs and 158 mg for ARBs. Although there is a slight increase in the mean daily dose of ramipril (4 mg versus 3.5 mg in 2011), the evidence-based dose of this disease-modifying drug according to the ESC guidelines should be 10 mg once daily.

Sacubitril/Valsartan

This new therapeutic class of drug was first introduced in the ESC guidelines from 2016 after a trial found this drug to be superior to ACEI in reducing hospitalization for worsening HF and cardiovascular mortality (2). Fourty-one percent of patients in this study were prescribed sacubitril/valsartan on discharge with a mean daily dose of 236 mg. However, for the majority of patients on this medication, during their last consultation, an increase in the dose was advised. The recommended daily dose according to ESC guidelines is 400 mg daily.

Beta-Blockers

Ninety-five percent of the patients in this study were discharged with a beta-blocker. This is significantly higher than 61% recorded in 2014 and 58.3% recorded in 2011. The guidelines recommend the use of beta-blockers and ACEI s as soon as the diagnosis of HFrEF is established as the two drugs acts complementary and reduces mortality and morbidity. The mean daily dose for beta-blockers has also increased. Bisoprolol was prescribed with a mean daily dose of 5.2mg compared to 2.8mg in 2011(18). Carvedilol daily dose increased from 26.1mg in 2011(18) to 32mg now.

MRA

Eighty-seven percent of the patients were prescribed MRAs on discharge. This is considerably higher than the 31% recorded in 2014(19) and 44.2% in 2011(18). The mean daily dose given was 34.2mg. Men were more likely to be prescribed eplerenone compared to women (44% men versus 30% women). The opposite was true for spironolactone (56% men versus 70% women). MRAs are only prescribed when the patients still remain symptomatic despite the use of beta-blockers and ACEI and/or have EF< 35%.

Diuretics

Eighty-nine percent of the patients in the study were discharged on diuretics. This is slightly higher than the previously recorded data in 2014(19) and 2011(18). Usual daily doses of loop diuretics in patients with heart failure ranges from 40-240mg. In our study the mean daily dose was 93mg .

Digoxin

Only 7.5% received digoxin compared to 30% of patients in 2011. That is in concordance with the recommendation from the latest ESC Guidelines on HF.

Ivabradine

This novel sino-atrial node inhibitor which is advocated as a treatment option for controlling heart rate in certain HF population was only used in 2.8% of patients. This could be explained by significant participation of the patient in the costs of this drug in Croatia.

Monitoring

All patients with chronic HF require regular monitoring. When examining the patients, clinical assessment of functional capacity, fluid status, cardiac rhythm and nutritional status of the patient should be done. Supplementary tests should look into serum urea, electrolytes, creatinine and eGFR. However, more importantly a review of medication must be done and the need for an increase in dose or changes due to possible side effects should be considered. If patients present with significant comorbidity or if their condition has deteriorated, more detailed monitoring should be pursued. The clinical status and stability of the patients will depict the frequency of monitoring, however, the ESC guidelines recommend a 6-monthly review of the patient unless the clinical condition or medication have changed. All the patients in this study were stable and were suggested for review in 6-9 months.

Discussion

According to the definition of an epidemic, heart failure can indeed be considered an epidemic of present day. Cardiovascular diseases are the leading cause of morbidity, mortality and hospitalization in Croatia. HF alone contributes to significant morbidity and mortality and is the 7th most common cause of death in Croatia (19). Although HF still has a high five-year mortality rate with tendency to increase with increasing age, in the last 15 years, Croatia has seen a 60% decrease in HF-related mortality. This trend can be attributed due to early diagnosis, improved treatment modalities and medications for HF and other cardiovascular diseases (20). The chronic care of patients with HF should be embedded within a multidisciplinary program. Both national and international guidelines advice on implementation of such programs to reduce mortality and morbidity within HF population. Guidelines place emphasis on lifestyle advice, usage of pharmacological evidence-based medications, monitoring at appropriate interval, education of the patient regarding the therapies and rehabilitation.

This study focused on the use of optimal medical therapy for patients with HFrEF. When comparing the results of the study with the results from previous study performed in 2011, the prescription for guideline recommended evidence-based optimal therapy for HFrEF significantly improved in the last 7 years. The rate of compliance of the physicians to adhere to optimal medical therapy is more in concordance with the guidelines now than in 2011.

This study documents an increase of close to 40% in prescribing beta-blockers to HF patients (95% versus 58% in 2011). This is 4% more than prescription rates for beta-blocker for HF patients in the UK in 2014, which showed a rate of 91% (previously 77% in 2011). There is also an increase in mean daily dose of beta-blockers prescribed to HF patients. Both bisoprolol (5.2 mg compared to 2.8 in 2011) and carvedilol (32 mg compared to 26.1 mg) doses increased, however the recommended target doses for these medications are much higher than the doses prescribed.

The use of MRAs in HF almost doubled since 2011 (87% versus 44.2% in 2011). According to the ESC guidelines, MRAs should be used in all symptomatic HFrEF patients with LVEF of 35% or less in spite of treatment with ACEI and a beta-

blocker. This is shown to reduce mortality and hospitalization from HF (2)(12)(13). Spironolactone is associated with dose-dependent sexual side effects and gynecomastia and therefore male patients may not always be willing to use this, however, eplerenone on other hand has a small charge associated with each prescription, which may be a financial burden for the patient. In this study, men were more likely to be prescribed eplerenone than spironolactone and the opposite was true for women. MRA usage in the UK increased from 44% in 2011 to 56% in 2014, which is significantly less than the current rates in Croatia.

ESC guidelines recommend the use lowest achievable dose of diuretics to maintain euvolemia in patients with HFrEF. Diuretics use also increased slightly since 2011 (88.8% versus 86.3% in 2011). The mean daily dose of furosemid (93 mg) is within the range (40-240 mg) recommended by ESC guidelines. Both UK and Croatia show similar rates of diuretics use in HF with an uptrend since 2011.

The use ACEIs has been showing a downtrend since 2011. Only 44% of the patients received ACEI compared to 48% in 2014 and 53% in 2011. Fifty-three percent of the patients received either an ACEI or an ARB on discharge. The downtrend is probably due to the introduction of a new therapy - sacubitril/valsartan in the ESC guidelines of 2016. In the PARADIGM-HF trial (10) the use of this therapy showed superiority over ACEI in patients with symptomatic HFrEF with LVEF ≤40% and elevated plasma NT-proBNP ≥600 pg/mL or patients who had been hospitalized for HF within the last 12 months. This population of the patients received sacubitril/valsartan (400 mg daily) that showed reduced mortality, morbidity and hospitalization rate for worsening HF. ESC guidelines therefore recommends the use of this therapy in patients who fit this profile (2). Forty-one percent of patients in this study received this therapy with mean daily dose of 236.4 mg.

There are certain areas of implementation in HF patients that need to be addressed. These include: firstly the use of optimal medical therapy, which was the main goal of this study, secondly follow-up and monitoring of HF patients, which are again clearly set in the guidelines and thirdly patient education and finally cardiac rehabilitation. The latter is an established part of the therapeutic intervention package in areas of cardiology such as post-MI and following a CABG procedure but despite being recommended and proven to have clear benefits for HF patients, it has been

relatively neglected within HF (23). In the audit of 2014 in the UK, the number of HF patients that were told about the benefits of regular cardiovascular exercise reached almost 100%, however, the number of patients that were referred or enrolled into a HF rehab program totaled less than 10% (23). Data throughout Europe shows similar findings and this can be attributed to geographical variations and lack of finances. Hence, the focus of the multidisciplinary team in charge of HF patients should be directed towards expanding and investment into rehabilitation services for HF patients.

Patient education at discharge is found to be vital to improved outcomes of HF. Education of patients or family members of HF patients and stressing the importance of medication adherence, sodium and fluid restriction and recognition of signs and symptoms of worsening HF early, are shown to reduce re-hospitalization rates of HF patients (24). Some estimates put the preventable readmission rates for HF patients at 54% and attributes lack of compliance with medication, lack of sodium and fluid restriction and failure of follow-up as the primary culprit for the high rate of re-hospitalization (25). Overall, patients who have not been educated about their disease and their medication are at a disadvantage. The management of a HF patient requires a multidisciplinary team, and cardiac nurses also play a fundamental role.

I believe the future lies in training cardiac nurse to take on primary practitioners role in educating and evaluating patients self-care abilities. These nurses can be trained to take on the role of educators and educate patients about their medication and diet and also how to adjust medication doses according to patient's fluid status and BP without coming to the hospital. For all this to happen a discharge management program needs to be instituted with evidence-based guidelines, where cardiac nurses take on the lead in educating patients and thus improving the level of care for HF patients.

Limitations

The study focused only on ambulatory patients of HF in the outpatient's clinic, which understandably does not represent the whole population, however, the data was randomly collected to avoid bias and to represent the population within this centre. Of course, since the data was collected from a single centre, it makes it subject to selection bias and thus not entirely generalizable to whole Croatia, yet the results displayed a general trend seen in previous studies on this topic. Furthermore, the results were directly compared with ESC guidelines without taking clinical monitoring of the patients into account. Further studies should take all the above-mentioned points into account by collecting the data nationwide to avoid selection bias.

Conclusion

This study demonstrated a significant improvement in optimal medical therapy for HF and an increased adherence of the physicians to the ESC guidelines. However, the target daily dose for most medication is still insufficient and remains below the recommended dose. An improvement in this area would certainly help in care of HF patients. In diagnosing HF, the use of NT-proBNP still remains very low. The multidisciplinary team in charge of HF patients must always strive to provide the best possible care for the patients. General physicians, internists and cardiologists should always aim to adhere to the guidelines and improve management of their patients by simple education of their patients about HF and its treatment, whereas, cardiac nurses should be encouraged to individualize discharge management and help with cardiac rehabilitation programs.

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Biography

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OBJECTIVE

A highly motivated, numerate and reliable medical student with strong academic record and keen interest in medicine. I have undertaken relevant work experience in health care sectors in different countries. Being able to speak four different languages fluently, and having vital work experience with both medical practitioners and patients, I believe I have all the qualities, aptitude and enthusiasm to make a positive contribution to your team.

KEY ATTRIBUTES

- **Multilingual (good conversational English, Dutch, Farsi, Hindi)**
- **A critical thinker with strong analytical skills.**
- **Strong team player**
- **Good organizational skills developed in a variety of deadline-orientated situations.**
- **Get on well with people at all levels, easily making good working relationships.**
- **Have good presentation skills combining sound analytical research and clear verbal explanation.**
- **Seek out new responsibilities irrespective of reward and recognition.**

EDUCATION

University of Zagreb, Medical school in English. Zagreb, Croatia 2012-Present

Doctor of Medicine

Expected Graduation: July 2018

Queen Mary University of London, London, UK 2009-2012

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HONORS & AWARDS

Dean's Commendation Award
2014

- For a distinguished academic record in 2013-2014

Rector's Award
2015

- For organising a fundraising and assembling a group of medical students to help the refugees at Croatian-Slovenian border in collaboration with SAR-EMS-Europe (Search and Rescue Europe and European Emergency Medical Services)

Professional & Volunteer Experience:

Addenbrookes NHS Trust Cambridge

- *General and Respiratory Medicine Department* **August-September 2017**
  - Supervisor: Dr. Clare Sander
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- *Accident and Emergency*
  - Volunteer

PROFESSIONAL MEMBERSHIP

- **CROSS – Croatian Student Summit**
  - The Croatian Student Summit is an international scientific congress of medical students and young scientists in the field of biomedicine

- **Student Cardiology Society – University of Zagreb**
- **Student Surgery Society – University of Zagreb**

PERSONAL INTERESTS

- Football
- Travelling
- Reading