Master Thesis

Prognosis of chronic heart failure based on data from the EuroHeart Failure Survey

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to achieve the academic degree

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Datum der Einreichung

Affirmation in lieu of an oath

I confirm on oath, that I have done the following work on my own and without other peoples' help. I have not used other than the specified references and I have accurately marked the text passages where I have used these references verbally or with regards to content.

Graz, Datum _____

Elisabeth Smolle

Acknowledgement

I want to thank my supervisor Professor Friedrich Fruhwald, who supported me at the best in writing this master thesis. Whenever I was uncertain about something, I could count on his back up. I also want to thank my secondary supervisor, Doctor Vesna Riegelnik, who especially supported me in my work with the patients' questionnaires.

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And last but not least I want to say "thank you" to all the people, who have made my studies a bright, joyful and simply unforgettable time!

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List of abbreviations

ACEI	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
AHF	Acute heart failure
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
BMI	Body mass index
BNP	Brain natriuretic peptide
CAD	Coronary artery disease
CHF	Chronic heart failure
CMR	Cardiac magnetic resonance imaging
COPD	Chronic obstructive pulmonary disease
CRT	Cardiac resynchronization therapy
CRT-P	Cardiac resynchronization therapy-pacemaker
CT	Computertomography
DCM	Dilative cardiomyopathy
DDD	Dual chamber pacing
ECG	Electrocardiogramm
EF	Ejection fraction
EHFS	EuroHeart Failure Survey
EHS/R	European Heart Survey and Registry Programme
EMB	Endomyocardial biopsy
EORP	EurObservational Research Programme
ESC	European Society of Cardiology
FUP	Follow-up
GFR	Glomerular filtration rate
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HNCM	Hypertrophic non-obstructive cardiomyopathy

HOCM	Hypertrophic obstructive cardiomyopathy
IQR	Interquartile range (statistics)
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal pro Brain Natriuretic Peptide
NYHA	New York Heart Association
SBP	Systolic blood pressure
WHO	World Health Organisation
dl	Decilitre
g	Gram
hb	Hemoglobin
kg	Kilogram
l	Litre
m	Metre
m^2	Square metre
mg	Milligram
ml	Millilitre
mmol	Millimol
pg	Picogram

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Zusammenfassung

Hintergrund

Die Herzinsuffizienz ist ein Krankheitsbild, das durch ventrikuläre Dysfunktion, Dyspnoe sowie häufig durch periphere Ödeme gekennzeichnet ist. Die Prognose der Erkrankung ist schlecht wobei unklar ist, wie die internationalen Guidelines in die Prasix umgesetzt werden (können). Um hier mehr Information zu gewinnen, wurde das EuroHeart Failure Survey, eine europaweite, multizentrische Studie, ins Leben gerufen. In dieser soll mehr Information über das Krankheitsbild „Herzinsuffizienz“ gesammelt werden.

Ich habe Daten von Patienten mit chronischer Herzinsuffizienz, die in das Survey eingeschlossen wurden, ausgewertet.

Material und Methoden:

Anhand von Fragebögen, die für das EuroHeart Failure Survey konzipiert wurden, habe ich die Daten der Patienten ermittelt. Da die Patienten bereits ein Jahr zuvor in das Survey aufgenommen wurden, handelt es sich um das 12-Monats Follow-up. Die Einschlusskriterien waren chronische Herzinsuffizienz jeglicher Genese und ein Alter von >18 Jahren. Insgesamt wurden so die Daten von 66 Patienten ermittelt. Die Patienten wurden entweder bei Routine-Kontrollen an der kardiologischen Ambulanz oder telefonisch kontaktiert.

Resultate:

Unter den 66 Patienten waren 15 Frauen und 51 Männer; das mediane Alter betrug 61 Jahre. Die durchschnittliche Richtlinientreue lag bei etwa 40%. Sie verbesserte sich innerhalb eines Jahres von 32% auf 50%. Durchschnittlich wurden Patienten mit Hauptwohnsitz in der Stadt besser behandelt, als jene mit Hauptwohnsitz am Land. Frauen wurden mit höherer Richtlinientreue behandelt als Männer (54% versus 37%). 13 Patienten wurden innerhalb der letzten 6 Monate rehospitalisiert. Von 66 überlebten 4 die Follow-up-Periode von einem Jahr nicht.

Diskussion und Schlussfolgerung:

Mit 94% liegt die 1-Jahres Überlebensrate relativ hoch. Dass sich viele Patienten innerhalb der Follow-up-Periode funktionell, d.h. hinsichtlich der NYHA-Klasse, verschlechterten, spricht für ein eingeschränktes Heilungspotenzial bei Herzinsuffizienz-Patienten. Die

Krankheit ist mit höherem Lebensalter vergesellschaftet und verläuft in vielen Fällen trotz adäquater Therapie progredient.

Abstract

Background:

Heart failure is a disease with ventricular disorder, dyspnea and, often, peripheral edema. Prognosis of these patients is bad and it is unclear how international guidelines can be implemented. To gain information in this context, the EuroHeart Failure survey, a multinational Euopean research programme has been implemented. The major intention was to gain information about managing heart failure patients in the real world.

I collected data from patients suffering from chronic heart failure taking part in the survey.

Material and Methods:

The patients' data was collected using questionnaires. I did the 12 months-follow up, because the patients have been included in the survey one year before. Inclusion criteria were chronic heart failure of any etiology and >18 years of age. 66 patients have been investigated. They have either been contacted at routine-investigations at the cardiological clinic of Graz or by telephone.

Results:

Among the 66 patients, there were 15 women and 51 men. The median age was 61 years. On average, guideline adherence was 40 % with an improvement from 32% at baseline to 50% at the 12 months-follow up. Patients living in the city were treated with better adherence than those living in rural areas. Women were treated in better adherence with the guidelines than men (54% versus 37%, respectively). 13 patients have been rehospitalized within the previous 6 months. 4 out of 66 patients did not survive until the 12 months-follow up.

Discussion and Conclusion:

One-year survival is relatively good with 94%. However, many patients deteriorated regarding the NYHA-functional classification. This suggests, that heart failure is a progressive disease, because advanced age contributes to clinical deterioration despite of good treatment. There is limited chance for complete healing.

1 Introduction

1.1 Basic Information about Chronic Heart Failure

1.1.1 Definition

According to the World Health Organisation (WHO), heart failure is defined by decreased physical capacity due to a ventricular disorder [1].

A probably more precise definition describes heart failure as being an inability of the heart to offer the required cardiac output for the body while the end diastolic pressure is normal [1].

The European Society of Cardiology (ESC) defines heart failure (HF) in its 2008-guidelines as follows: "Patients suffering from heart failure typically have the following features: dyspnea at rest or during physical exercise and/or fatigue, fluid retention (e.g. in the lung and ankles), morphological and functional alterations of the heart [2]."

Summing up these three definitions, heart failure includes three main signs, namely shortness of breath, fluid retention and morphological signs of cardiac damage.

The American College of Cardiology/American Heart Association [3] classifies the progression of heart failure in 4 stages (A-D):

A) No signs of heart failure; risk factors present; e.g. hypertension, coronary artery disease (CAD)

B) No symptoms, signs of left ventricular dysfunction in the echocardiography (hypertrophy, dilation, valvular heart disease)

C) Symptomatic heart failure: Dyspnea (at rest or with exertion), fluid retention

D) Advanced heart failure with severely decreased inotropy; assist device or heart transplant is considered

1.1.2 Classification

Systolic and diastolic heart failure

Systolic heart failure is distinct from the diastolic form. Patients with diastolic heart failure have signs/symptoms of heart failure with a preserved ejection fraction (EF=stroke volume/end-diastolic volume of the relevant ventricle). There is no clear consensus about the cutoff for "preserved EF" (approximately >40-50%). Systolic heart failure is characterized by a reduced ventricular ejection fraction due to an impairment of the myocardial contraction. Although distinction between these two types of HF is wanted by physicians it is not possible in each and every patient simply because both forms can occur together, either at rest or during exercise [2].

Chronic and acute heart failure

Heart failure is a chronic illness (chronic heart failure, CHF), but worsening of the symptoms can lead to rehospitalization or more frequent doctor visits (decompensation of CHF) [4]. For some reasons, however, signs of heart failure can develop rapidly (severe symptoms and signs of heart failure within 24 hours), which is defined as acute heart failure (AHF).

Usually, patients suffering from acute heart failure present in one of six clinical categories [2]:

- Acute decompensated CHF
- Pulmonary edema
- Hypertensive acute heart failure
- Cardiogenic shock
- Isolated right HF
- Acute coronary syndrome (ACS) and HF

AHF patients often have more than one of these features, so any classification will have its limitations.

1.1.3 Epidemiology

Heart failure mainly concerns elder people. In people younger than 50 years heart failure is rare with an increasing prevalence in the following years to come [4]. According to the Rotterdam study, the prevalence of heart failure is 1% in age group 55–64 years, 3% in age group 65–74 years, 7% in age group 75–84 years, and over 10%

in those aged >85 years [5]. According to Ho et al, the incidence of heart failure in the population of the Framingham-study was 1,4/1000/year for women and 2,3/1000/year for men. (Ho reported a heart failure prevalence of 0,8% in this population) [6].
In Austria about 27.000 patients are hospitalized every year because of heart failure compared to 12.000 patients suffering a myocardial infarction. About 24.000 of those suffering from heart failure are aged >65. Heart failure patients older than 65 form eight-times the number of heart failure patients in all age groups ≤65 put together. The average period of hospitalization because of heart failure is 10 days (compared to 8 days in myocardial infarction) [7].

1.1.4 Etiopathogenesis of Chronic Heart Failure

1.1.4.1 Etiology

1.1.4.1.1 Ischemic Heart Failure

Ischemic heart failure is myocardial dysfunction due to insufficient perfusion. This is caused by CAD, a subtype of arteriosclerosis affecting the coronary vessels. The etiology of CAD comprises several cardiovascular risk factors, namely little physical activity, an "unhealthy diet" high in fat and calories and smoking. Coronary arteries narrow, resulting in hypoperfusion of the myocardium leading either to hibernation (temporarily) or myocardial infarction (definite).

1.1.4.1.2 Non-ischemic Heart Failure

Non-ischemic heart failure can be caused by longstanding hypertension, myocarditis, cardiomyopathies or drugs and toxins harming the myocardium (e.g. ethyl-alcohol, cytotoxic agents, cocaine), endocrine diseases such as a pituitary adenoma producing human growth hormone, qualitative and quantitative malnutrition or extreme obesity and infiltrative diseases (e.g. hemochromatosis).

1.2 Diagnosis

In 1933 Sir Thomas Lewis wrote in his textbook on heart disease, that it is most essential in cardiovascular medicine to detect heart failure in an early stage [8]. Symptoms of cardiac deterioration (e.g. breathlessness, chronic fatigue) make patients visit a doctor; so these symptoms are the key to heart failure diagnosis.

Clinical diagnosis: In early stages, left-sided heart failure can be determined from right-sided heart failure (e.g. pulmonary edema versus ankle-edema). In advanced stages, discrimination between left- and right-sided HF only by clinical investigation is hardly possible.
Persistent or worsening symptoms after several weeks of treatment may indicate bad prognosis. However, the link between symptoms and severity of cardiac dysfunction is loose [2].

The 6-minute walking test is easy to perform and reproducible and, therefore, useful to examine the response to therapy in follow ups. In this test, patients have to walk as far as they can within 6 minutes. The distance is compared to standard values dependent on age, bodyweight and gender. Therewith, improvement and deterioration in physical capacity can be assessed.

The New York Heart Association (NYHA) functional classification based on breathlessness/dyspnea is commonly used to classify the severity of heart failure:

- NYHA I: No dyspnea or other signs of heart failure. LV-dysfunction present on echocardiography
- NYHA II: Dyspnea at heavy exertion
- NYHA III: Dyspnea at slight exertion
- NYHA IV: Dyspnea at rest

The NYHA-functional class III or IV is a powerful predictor for poor prognosis [2].

Chemistry: At present, the best parameter for myocardial stress is B-type natriuretic peptide (BNP) or its N-terminal fragment (NT-pro BNP). An NT-pro BNP >2000 pg/ml makes heart failure likely in untreated patients, a value <400 pg/ml makes this diagnosis rather unlikely [2]. Hyponatremia, renal dysfunction (elevated creatinine and urea, reduced glomerular filtration rate) and an elevation of troponin commonly occur in symptomatic heart failure as well.

Instrumental diagnosis:

Electrocardiography (ECG) can display all sorts of pathology in heart failure patients. There is no “heart failure specific” ECG.

Chest X-ray (in two planes) is used to detect cardiomegaly, pleural fluid retention and pulmonary diseases contributing to dyspnea.

Echocardiography, the sonography of the heart, can measure ventricular diameter and thickness of the wall; the ejection fraction and contractility can be evaluated. Furthermore, a possible valvular regurgitation/stenosis should be examined. Exploration of the pericardium is also possible.

Cardiac magnetic resonance imaging (CMR) has become the gold standard to assess volumes, global function, regional wall movement, thickening of the wall, valvular pathology and pericardial abnormalities.

Computertomographical (CT-) Angiography of the coronaries may be useful in patients with suspected CAD causing myocardial ischemia.

Cardiac catheterization is useful to measure the intracardiac pressure at rest and at exertion. There is left heart catheterization, including coronary angiography, and right heart catheterization giving precise hemodynamic information (filling pressure, cardiac output, vascular resistance).

In fulminant heart failure of unknown etiology with rapid deterioration endomyocardial biopsy (EMB) can be made, which may help to detect the reason.

1.3 Recommended Therapy

The guidelines for heart failure treatment by the ESC provide principles in pharmacologic, but also in non-pharmacologic therapy. Every physician should conform to the guidelines of treatment of a certain disease, as good adherence has been shown to be beneficial for the patients' prognosis [9].

1.3.1 Non-pharmacological Therapy

Non-pharmacological therapy comprises self care management at first place. This includes the patient's awareness for deterioration of heart failure, weight monitoring, minor sodium intake, controlled fluid intake, little alcohol, no smoking and regular moderate exercising. These measures aim to stabilize the patient with heart failure, so his physical capacity is preserved as long as possible. Risk factors for deterioration shall be reduced and signs of worsening shall be detected early.

Percutaneous coronary intervention (PCI):

PCI is indicated in selected heart failure patients with CAD. The decision between PCI and bypass grafting is based on careful evaluation of co-morbidities and procedural risk. Viable myocardium must be detected, because this is the aim for revascularization. Furthermore, the degree of left ventricular dysfunction and the presence of valvular disease must be considered [2].

Surgical bypass grafting:

In symptomatic CAD, surgical bypass grafting is possible to relief chest pain. However, according to the STICH-trial, where possible benefits of bypass grafting in patients with ischemic heart failure was examined, there was no significant improve in mortality in patients with bypass grafting and medical therapy compared to patients with medical therapy alone [9].

Valvular surgery:

This is an option when valvular dysfunctions are responsible for heart failure symptoms causing hemodynamic instability. However, impaired LVEF is associated with higher peri- and postoperative mortality and is therefore a risk factor, that has to be considered [2]. A patient's risk profile and motivation have to be considered carefully before the intervention.

Cardiac resynchronisation therapy (CRT) and implantable cardioverter defibrillator (ICD):

In patients with heart failure in NYHA-classes II-IV, a broad QRS-complex (120 msec or more) and a reduced LV-EF, the implantation of a cardiac resynchronisation therapy (CRT) is indicated. According to the SCD-HeFT trial, patients with NYHA-class II or III and CHF single-lead, shock-only ICD therapy reduces overall mortality by 23 percent [10]. In selected patients, a combination of CRT with an ICD is the device-treatment of choice.

1.3.2 Pharmacological Therapy

According to the current ESC-guidelines the basics of pharmacological heart failure management can be summed up to this:

Unless contraindicated or not tolerated,

- An **ACEI** should be prescribed in all patients with symptomatic HF and a LVEF ≤40% [2].

- An **ARB** is recommended in patients with HF and a LVEF ≤40%, who remain symptomatic despite optimal treatment with an ACEI and β-blocker [2].

- Every patient with symptomatic heart failure should have an ACEI or/and an ARB. If an ARB is used in combination with an ACEI, it is important to monitor serum electrolytes and renal function regularly [2].

- All patients with heart failure and an LVEF ≤40% must be prescribed a **β-blocker** [2]. Additionally to treatment with ACEIs and ARBs, a β-blocker has to be prescribed in all HF patients.

- The addition of a low-dose **aldosterone antagonist** should be considered in all patients with an LVEF ≤35% and severe symptomatic HF, i.e. currently NYHA-functional class III or IV [2]. This means, that above NYHA-functional class II, it is obligatory to add an aldosterone antagonist in combination with ACEI/ARB and β-blocker.

- Diuretics are recommended in patients with HF, who suffer from fluid retention [2].

For some drugs frequently used in heart failure, there are target doses given in the ESC guidelines (plus starting doses and suggestions how to titrate the dosage). In diuretics, the recommended dosages are only approximate values. The amount of fluid retention is the most important variable for dosage adjustment.

	Starting dose	Target dose (mg)
ACEIs		
Captopril	6.25 t.i.d.	50-100 t.i.d.
Enalapril	2.5 b.i.d.	10-20 b.i.d.
Lisinopril	2.5-5 o.d.	20-35 o.d.
Ramipril	2.5 o.d.	5 b.i.d.
ARBs		
Candesartan	4 or 8 o.d.	32 o.d.
Valsartan	40 b.i.d.	160 b.i.d.
Aldosterone antagonists		
Spironolactone	25 o.d.	25-50 o.d.
Eplerenone	25 o.d.	50 o.d.
β-blockers		
Bisoprolol	1.25 o.d.	10 o.d.
Carvedilol	3.125 b.i.d.	25-50 b.i.d.
Metoprolol succinate	12.5-25 o.d.	200 o.d.
Nebivolol	1.25 o.d.	10 o.d.

Table 1: Starting and target dosages of frequently used heart failure medication recommended by the ESC. Modified according to table 20 from the "ESC Guidelines of the diagnosis and treatment of acute and chronic heart failure 2008" [2].

	Usual daily dose (mg)
Furosemide	40-240
Torasemide	10-20
Hydrochlorothiazide	25-100

Table 2: Recommendations for diuretic dosages in heart failure by the ESC. [2]

1.4 Prognosis

The prognosis of heart failure is poor with reported survival estimates of 50% and 10% at 5 and 10 years, respectively [11-14].

According to the ESC-guidelines the following conditions are associated with poor prognosis:

Demographics	**Clinical features**	**ECG**	**Functional**	**Laboratory**	**Imaging**
Old age	Hypotension	Tachycardia Q-waves	Reduced work, low peak VO_2	Considerable NT-pro BNP elevation	Low LVEF
Ischemic etiology	NYHA-functional class III-IV	Wide QRS	Poor 6-minute walk distance	Hyponatremia	
Resuscitated sudden death	Prior hospitalization because of HF	Signs of left ventricular hypertrophy		Elevated troponin	
		Complex ventricular arrhythmia			

Table 3: Strong predictors for poor prognosis in heart failure (modified according to the ESC guidelines 2008). [2]

Other circumstances associated with an unpromising outcome, mentioned by the ESC, are:

- Kidney dysfunction (elevated creatinine and urea, reduced glomerular filtration rate)
- Diabetes mellitus
- Anemia (defined by reduced hemoglobin)
- COPD
- Depression
- Low body mass index
- Aortic valve stenosis
- Poor compliance

1.5 The EuroHeart Failure Survey

It is the mission of the ESC to "reduce the burden of cardiovascular disease in Europe" [2].

Since 1999 the ESC has implemented an International clinical research programme, Euro Heart Survey & Registry Programme (EHS/R). In 2009, a new programme of surveys & registries was launched: EURObservational Research Programme (EORP) [15].

The Euro Heart Failure Survey is one of the pan-European surveys of the EORP. It is the first pan-European survey with the aim to gain information about patients hospitalized for heart failure. The analysis of clinical features and treatment of the heart failure patients may help detecting opportunities for improved diagnosis and therapy [16]. In October 2009, the ESC-HF Pilot study has started. It is a prospective, multicentre, observational survey with 12 European countries participating. A total of 136 cardiology centres have joined in. The aim is to evaluate HF-treatment in everyday clinical practice focusing on distinctions between the countries and on divergences from the ESC-recommendations.

Territorial subdivision was made, forming 4 groups of countries:

I) 4 Western European countries (Austria, France, Germany and The Netherlands)
II) 2 Eastern European countries (Romania and Poland)
III) 3 Southern European countries (Greece, Italy and Spain)
IV) 3 Northern European countries (Denmark, Norway and Sweden)

The number of participating centres for each country was decided according to the number of inhabitants. One centre per 2 million inhabitants was required, but no more than 25 and no less than 6 centres per country [17].
Furthermore, in every country there should be a balanced proportion between centres with different infrastructure: The clinical centres were distinct in those with cardiac surgery, those with interventional cardiology (such as percutaneous coronary intervention) and those without surgery or interventional cardiology.

For Austria, there is/are:
1 centre with cardiac surgery: University clinical centre of Graz

2 centres with cardiology: Saint Josef hospital (Braunau), Hospital "Elisabethinen" (Linz)

3 centres without surgery or cardiology: Hospital "Barmherzige Brüder" (Graz), General hospital Tulln, General hospital Feldbach.

Patient data has now been collected all across Europe for a period of 12 months and analysis is in process.

2 Patients and Methods

2.1 Inclusion Criteria

All outpatients with chronic heart failure diagnosed by the responsible cardiologist at the participating centre, were included in the survey about chronic heart failure [17]. In the clinic of Graz, diagnosis is normally based on clinical investigation, ECG, echocardiography (EF) and supported by the laboratory parameter NT-proBNP.

Furthermore, a population of acute heart failure was investigated (patients admitted to hospital with acute heart failure, who needed intravenous therapy).

Apart from this, there was only one other inclusion criterion, namely the patient's age >18.

2.2 Data Collection

Baseline:
Patients with chronic heart failure were investigated in October 2009, who fulfilled inclusion criteria and who agreed with participating. They had to sign a consent form.
After that, basic information was collected, e.g. blood pressure, height, weight, NYHA-functional class. Etiology of heart failure was documented.

The clinical history was registered (risk factors, co-morbidity, device therapy).

Routine clinical investigations were documented (physical status, chemistry, ECG, Chest X-ray, Echo-Doppler, Exercise test,…). If a certain examination was not scheduled, there was no need to do it for the survey; it is the aim of a survey only to document clinical routine without manipulating it.
There were different registry sheets for outpatients and hospitalized patients, respectively.

Current medication was documented prior to the outpatients' visit and after adapting medication by the cardiologist (= after discharge).

3- and 6 months-follow ups covered the vital status and rehospitalization since baseline investigation. Normally, the NYHA-functional classification was recorded; in case of death, mode and cause were documented.
In October 2010, I started the 12 months-follow up to compare this data to the data which has been surveyed at baseline.

12 months-follow up:
The 12 months-follow up comprised the same features, and additionally chemistry (if a laboratory examination was made) and current medication.

Heart Failure Pilot Registry

12 Month Follow-Up

Status at 12 months post inclusion

Lost to follow-up: ☐

Contact date: |__/__/____| *dd/mm/yyyy*

Where is collected the data: |__| *1 - Hospital*
2 - Primary care
3 - HF clinic
4 - Other organisation

By whom: |__| *1 - Cardiologist*
2 - GP
3 - Internal medicine doctor
4 - Geriatrician
5 - Nurse
6 - Physiotherapist
7 - Palliative care nurse
8 - Other

Vital status: ☐Alive ☐Dead

If Dead, Date of death: |__/__/____| *dd/mm/yyyy*

Cause of death: |__| *1 – Procedure related*
2 – Non procedure related
3 – Unknown

|__| *1 - Cardiac*
2 - Vascular
3 – Non cardiovascular
4 – Unknown

If Cardiac cause: Mode: ☐Sudden ☐Non-sudden
Cause: ☐AMI ☐Heart Failure ☐Arrhythmia ☐Other

If other cardiac cause, please specify: |_____|

If Vascular cause, |__| *1 – Ischemic stroke*
2 – Hemorrhagic stroke
3 – Systemic hemorrhagy
4 – Peripheral embolism
5 – Pulmonary embolism

If Alive, NYHA class: ☐NYHA I ☐NYHA II ☐NYHA III ☐NYHA IV

Fig. 1: EHFS data sheet; 12-months FUP: Status at 12 months post inclusion.

Re-hospitalisation (since 6 month follow-up):

Re-hospitalisation		Date of hospitalisation	Primary Cause *1 – Cardiac, non HF* *2 – HF* *3 – Vascular* *4 – Renal dysfunction* *5 – Non CV*
#1	☐No ☐Yes	|__/__/____| *dd/mm/yyyy*	|__|
#2	☐No ☐Yes	|__/__/____| *dd/mm/yyyy*	|__|
#3	☐No ☐Yes	|__/__/____| *dd/mm/yyyy*	|__|
#4	☐No ☐Yes	|__/__/____| *dd/mm/yyyy*	|__|
#5	☐No ☐Yes	|__/__/____| *dd/mm/yyyy*	|__|

CHEMISTRY

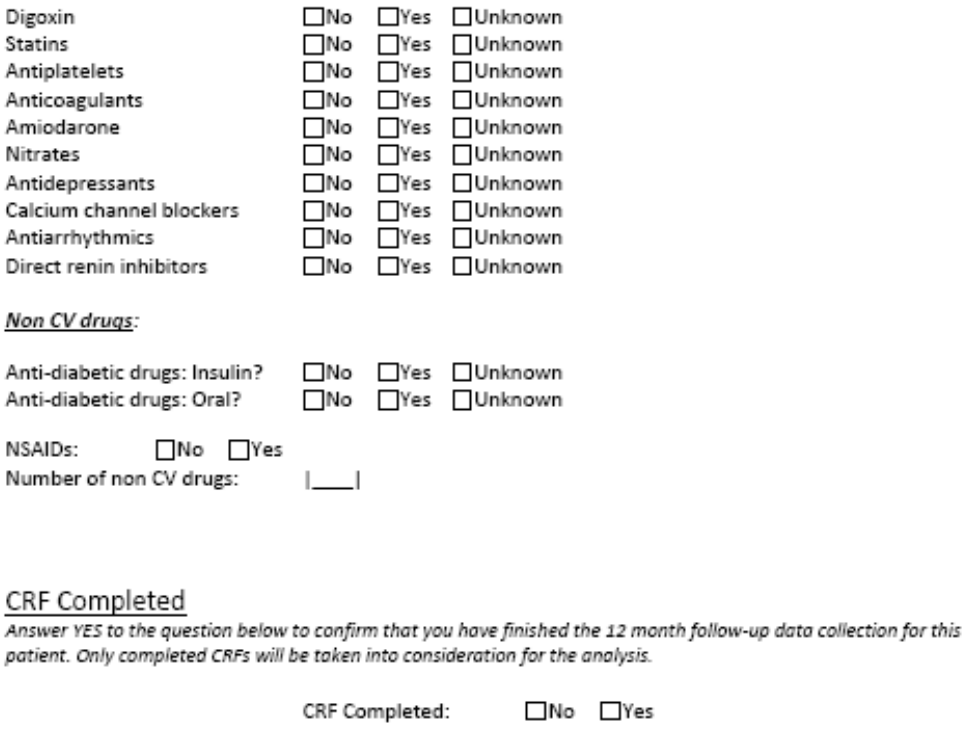
Hb:	|_____|	☐g/dL	☐mmol/L	☐g/L
Fasting glucose:	|_____|	☐mg/dL	☐mmol/L	
S-creatinine:	|_____|	☐mg/dL	☐µmol/L	
Sodium:	|_____|	☐mEq/L	☐mmol/L	
Potassium:	|_____|	☐mEq/L	☐mmol/L	
BNP:	|_____|	☐pg/mL	☐pmol/L	
NT-proBNP:	|_____|	☐pg/mL	☐pmol/L	

Nitrogen measured by: ☐BUN ☐Urea BUN: \|_____\| ☐mg/dL ☐mmol/L
Urea: \|_____\| ☐mg/dL ☐mmol/L

MEDICATION

Drug Type	*Generic Name*	*Total Daily Dose*		
ACE inhibitors	|__|	Total Daily dose: |_____| *mg*		
	1 - No	*2 – Benazepril*	*3 – Captopril*	*4 – Cilazapril*
	5 – Enalapril	*6 – Fosinopri*	*7 – Imidapril*	*8 – Lisinopril*
	9 – Moexipril	*10 – Perindopril*	*11 – Quinapril*	*12 – Ramipril*
	13 – Trandolapril	*14 – Zofenopril*	*88 - Other*	
Angiotensin II Receptor blockers (ARB)	|__|	Total Daily dose: |_____| *mg*		
	1 - No	*2 – Candesartan*	*3 – Eprosartan*	*4 – Irbesartan*
	5 – Losartan	*6 – Telmisartan*	*7 – Valsartan*	*88 - Other*
Beta blockers	|__|	Total Daily dose: |_____| *mg*		
	1 – No	*2 – Acebutolol*	*3 – Atenolol*	*4 – Bisoprolol*
	5 – Betaxolol	*6 – Carvedilo*	*7 – Celiprolol*	*8 – Labetalol*
	9 – Metoprolol	*10 – Nadolol*	*11 – Nebivolol*	*12 – Pindolol*
	13 – Propranolol	*14 - Sotalol*	*15 – Timolol*	*88 - Other*
Aldosterone antagonists	|__|	Total Daily dose: |_____| *mg*		
	1 - No	*2 – Spironolactone*	*3 – Eplerenone*	*4 – Canrenone* *88 - Other*
Diuretics N° 1	|__|	Total Daily dose: |_____| *mg*		
N° 2	|__|	Total Daily dose: |_____| *mg*		
	1 - No	*2 – Bendrofluazide*	*3 – Chlorthalidone*	
	4 – Hydrochlorotiazide	*5 – Furosemide*	*6 - Indapamide*	
	7 – Torasemide	*8 – Blumetanide*	*88 - Other*	

Fig. 2: EHFS data sheet; 12 months-FUP: Rehospitalization (in the previous 6 months), chemistry, medication.



Digoxin	☐No	☐Yes	☐Unknown
Statins	☐No	☐Yes	☐Unknown
Antiplatelets	☐No	☐Yes	☐Unknown
Anticoagulants	☐No	☐Yes	☐Unknown
Amiodarone	☐No	☐Yes	☐Unknown
Nitrates	☐No	☐Yes	☐Unknown
Antidepressants	☐No	☐Yes	☐Unknown
Calcium channel blockers	☐No	☐Yes	☐Unknown
Antiarrhythmics	☐No	☐Yes	☐Unknown
Direct renin inhibitors	☐No	☐Yes	☐Unknown

Non CV drugs:

Anti-diabetic drugs: Insulin?	☐No	☐Yes	☐Unknown
Anti-diabetic drugs: Oral?	☐No	☐Yes	☐Unknown

NSAIDs: ☐No ☐Yes

Number of non CV drugs: |___|

CRF Completed

Answer YES to the question below to confirm that you have finished the 12 month follow-up data collection for this patient. Only completed CRFs will be taken into consideration for the analysis.

CRF Completed: ☐No ☐Yes

Fig. 3: EHFS data sheet; 12-months FUP: Non HF-specific cardiovascular medication, non cardiovascular drugs.

Patients have been consulted either at routine checkups in the cardiological clinic of Graz or they have been contacted by telephone. At the 12 months-follow up, most patients have been questioned by phone, because their checkups where scheduled too far apart from the required follow up date (+/- 1 month). The patients' telephone numbers and anamnestic information have been gathered via MEDOCS, the central electronic documentation tool at general hospitals in Styria. Some patients could not be reached on their given phone numbers, so their family doctor or relatives were aksed instead. In case of a patients having died within the observational period, the municipal office of his/her habitation was consulted to gather the date, cause and mode of death.

2.3 Data Analysis

The results comprise descriptive statistics about 66 patients suffering from chronic heart failure.

Data were analyzed using Microsoft Excel. At first, I typed in all the data I evaluated with the questionnaire. After that, I formed groups in the metrically scaled variables:

- Age and NT-proBNP were subdivided in "below and above the median", i.e. age: ≤61 and >61; NT-pro BNP: ≤1199 pg/ml and >1199 pg/ml

- The cutoff for impaired EF was made <35% (≥35% = preserved EF)
- The cutoff for overweight was made at a body mass index (BMI) >25 kg/m^2 (≤25 = normal weight)
- For the laboratory parameters, the standard values from the University clinical centre of Graz were taken

Rehospitalization means, that the patient was rehospitalized in the previous 6 months (i.e. between the 6- and the 12 months-follow up). Some patients were rehospitalized more than once in this period (maximum: three times). I categorized rehospitalization in yes/no.

Patients were also categorized with respect to their living area in "city of Graz" and "countryside". This parameter was gathered via the patients' MEDOCS-record. This was made to evaluate differences in treatment between these two groups.

A variable called "guideline-adherence" included basics in heart failure therapy, namely:

- In NYHA I-II: ACEI or ARB and β-blocker
- In NYHA III-IV: ACEI or/and ARB and β-blocker and aldosterone antagonist

Overall, 66 patients (15 female, 23% and 51 male, 77%) were included in the analysis. Their median age was 61 with an IQR of 52-70. Since there are not all parameters available for every patient n <66 for most of the evaluations and also in the subgroups, missing data may cause little differences in the number of patients.

3 Results

3.1 Therapy

My aim was to evaluate the guideline adherence in patients at the cardiological clinic of Graz. As mentioned above, guideline adherence is defined as ACEI or/and ARB and β-blocker in NYHA-classes I and II plus aldosterone antagonist in classes 3 and 4. If patients in classes 1 and 2 received an aldosterone antagonist, this was defined as over-treatment and as a lack of guideline adherence.

3.1.1 Pharmacological Therapy

3.1.1.1 Medication at Baseline and at the 12 months-Follow up

I found, that treatment improved over the 12-month period in most patients. Despite of this, the NYHA-functional classification deteriorated in many patients, suggesting that heart failure is a progressive disease (see chapter 3.2.2).

3.1.1.1.1 ACEI and ARB

This parameter was available for 64 patients at baseline (ACEI and ARB) and for 62 patients (ACEI) and accordingly 63 patients (ARB) after 12 months.

Out of 64 patients, 43 had an ACEI at baseline, whereas 43 out of 62 were treated with this drug after 12 months. This is a slight improvement from 67% to 69%. An ARB was given to 11 out of 64 patients at baseline and to 16 out of 63 after 12 months . It has to be considered however, that an ARB is mostly given instead of an ACEI, because ACEIs may cause dry cough in 2-20% [18].

Altogether, 54 out of 64 received an ACEI or/and an ARB at baseline (84%) and 58 out of 63 were treated like this at the 12 months-follow up (92%).

3.1.1.1.2 Beta Blockers

This parameter was available for 65 patients at baseline and for 63 patients after 12 months.

β-blockers are an obligatory part of heart failure therapy in all NYHA-functional classes. Interestingly, β-blockers are even more established than ACEIs, as 58 out of 65 patients received this pharmaceutical (91%) at baseline. After 12 months, even 60 out of 63 patients (i.e. 95%) had a β-blocker.

3.1.1.1.3 Aldosterone Antagonists

This parameter was available for 65 patients at baseline and for 63 patients after 12 months.

An aldosterone antagonist should be used in all heart failure patients in NYHA-functional classification III and IV, unless contraindicated and in the absence of hyperkaliemia and severe renal dysfunction. Furthermore, this pharmaceutical may be beneficial for an LVEF ≤35% [2].

37 out of 65 patients (57%) were given an aldosterone antagonist at baseline; after 12 months, 41 out of 63 had this therapy (65%).

3.1.1.1.4 Diuretics

This parameter was available for 63 patients at baseline and for 60 patients after 12 months.

At baseline, 41 out of 63 patients (65%) were treated with a diuretic agent. After 12 months, 47 out of 60 patients (78%) had a diuretic therapy. Furosemide was the most commonly prescribed agent, accounting for 73% of all diuretics at baseline and for 62% at the 12 months FUP. Patients not receiving Furosemide either had Torasemide, Hydrochlorothiazide or Xipamide.

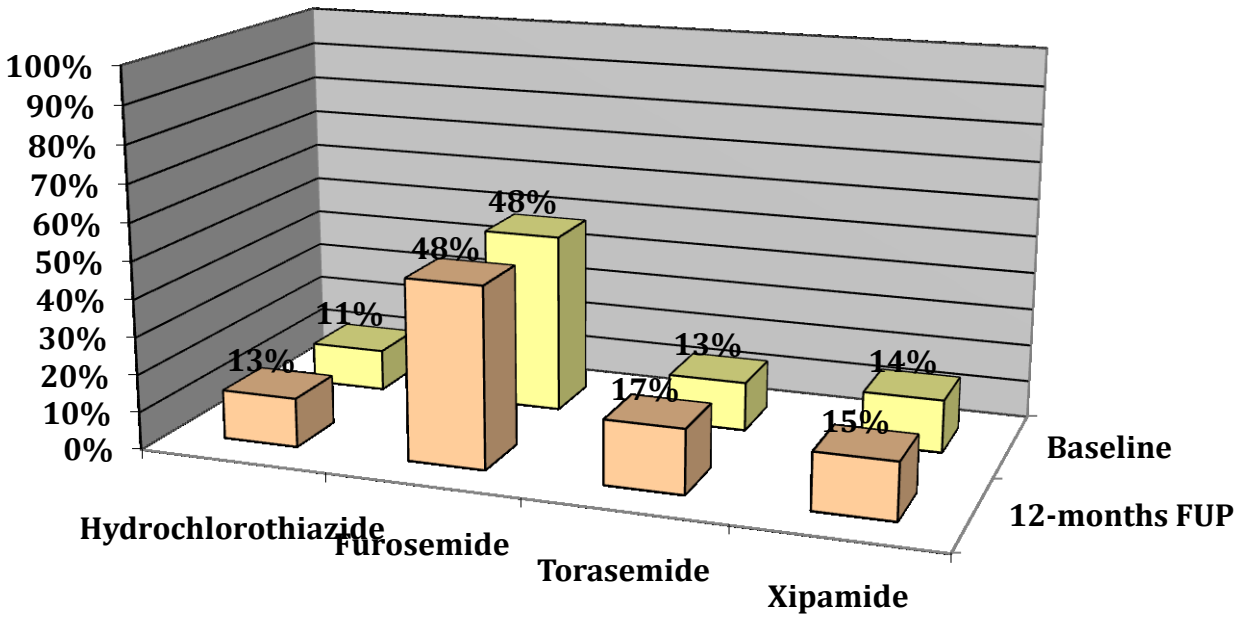


Fig. 4: Prescription of diuretic substances at baseline and after 12 months. It has to be considered, that some patients were treated with more than one diuretic agent.

3.1.1.1.5 Concomitant Medication (Statins, Amiodarone, Anti-thrombotics, Anti-diabetics)

In the EHFS-patients, 36 out of 65 (55%) had statin therapy at baseline. At the 12 months-FUP, 40 out of 63 (63%) received statins.

Amiodarone was given to 4 out of 65 patients (6%) at baseline and to 6 out of 63 patients (10%) after 12 months.

Anticoagulants were given to 32 out of 65 (49%) of the patients at baseline and to 31 out of 63 (49%) after 12 months. Antiplatelet agents were prescribed in 20 out of 63 patients (32%) at baseline, whereas 14 out of 62 (23%) had antiplatelet therapy after 12 months.

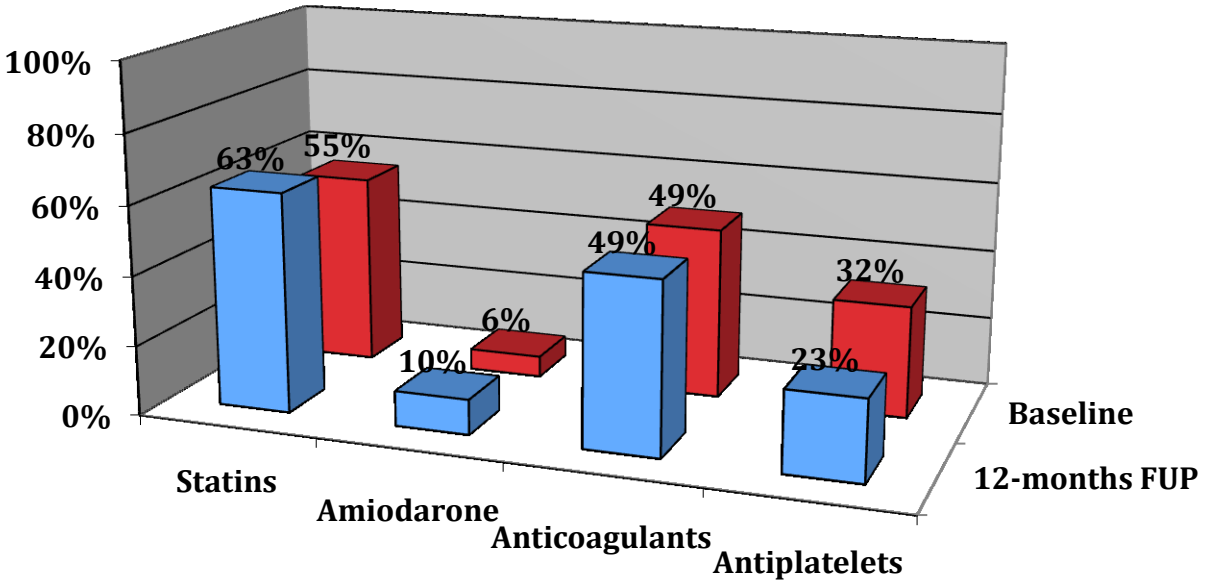


Fig. 5: Treatment with statins, amiodarone, anticoagulants and antiplatelets at baseline and after 12 months.

I reported anti-diabetic medication (i.e. metformin, sulfonylurea and insulin) in13 out of 66 patients (20%) over the follow-up period; i.e. the percentage of patients receiving an anti-diabetic therapy either at baseline or at the 12 months-FUP or both.

3.1.1.1.6 Additional Non-cardiovascular Medication

Patients were asked about their additional non-cardiovascular medication (e.g. bronchospasmolytic agents, acid blockers/proton pump inhibitors, antidepressants) at the enrolment and at the 12 months-FUP. It was not specified, what kind of medication they had. I subdivided the patients into 3 groups:

At baseline, 48 out of 65 patients (74%) received less than 3 (0-2) additional drugs. 16 patients (25%) were prescribed 3-5 additional drugs and 1 patient (1%) had more than 5 non-cardiovascular pharmaceuticals.

After 12 months, 45 out of 63 patients (72%) were given 0-2 additional drugs, 14 (22%) had 3-5 and 4 patients (6%) more than 5 additional pharmaceuticals.

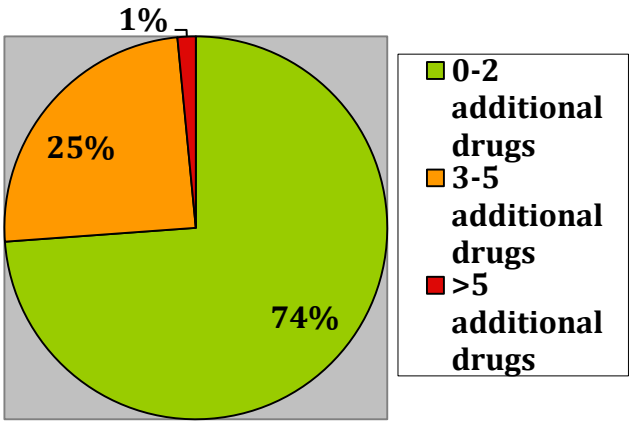


*Fig. 6: Patients treated with 0-2, 3-5 or more than 5 additional, non-cardiovascular drugs **at baseline.** n=65.*

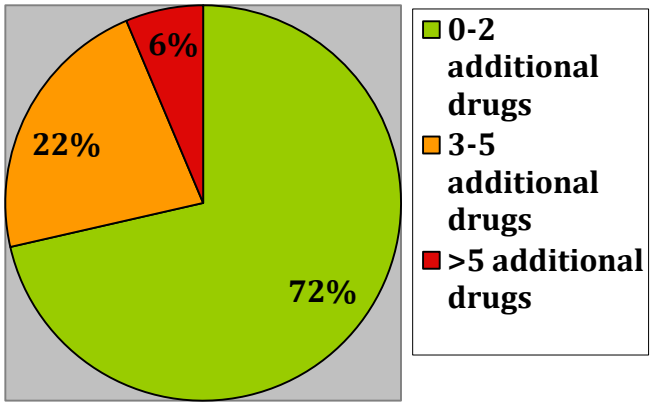


*Fig.7: Patients treated with 0-2, 3-5 or more than 5 additional, non-cardiovascular drugs **at the 12 months-follow up.** n=63.*

3.1.1.2 Guideline Adherence

On the basis of the ESC-Guidelines for heart failure therapy, I evaluated guideline adherence in the patients.

A very simple definition of guideline adherence is, that patients in NYHA-class I and II should be treated with an ACEI or/and an ARB and a β-blocker, whereas patients in NYHA-class III and IV must get the same drugs and, additionally, an aldosterone antagonist.

At baseline, 18 out of 60 patients (30%) fulfilled the criteria for treatment according to guidelines mentioned above. In the age-group 18-61 years, 9 patients out of 28 (32%) were treated in adherence with the guidelines and 10 patients out of 32 (31%) in the age-group >61 years. I found a difference in treatment between patients living in the city of Graz compared to those living in the countryside: 10 out of 46 patients living in

rural areas (22%) were treated according to the guidelines whereas 9 out of 14 patients living in the city (64%) had guideline adherent therapy. Regarding functional impairment, 12 out of 43 patients (28%) in NYHA-functional classes I and II were treated according to the guidelines while in NYHA-functional classes III and IV, 6 out of 16 patients (38%) received the recommended therapy.

After 12 months, 30 out of 60 patients (50%) were treated with good adherence, which means an improvement of 18% within 12 months. 13 out of 28 patients aged between 18 and 61 (46%) had guideline adherent therapy and so had 17 out of 32 (53%) in the patients aged >61. There was good adherence in 23 out of 46 patients living in the countryside (50%) and in 7 out of 14 living in the city of Graz (50%). Recommended therapy was prescribed in 12 out of 33 patients (36%) in NYHA-functional classes I and II and in 18 out of 27 patients (67%) in NYHA-classes III and IV.

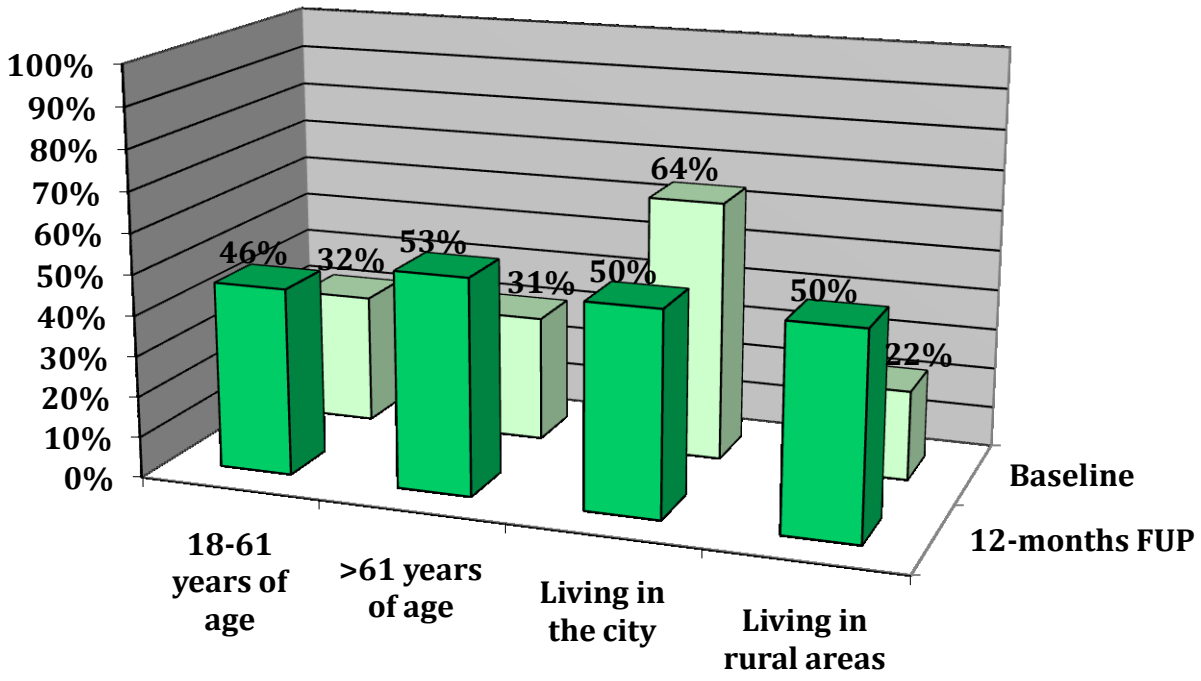


Fig. 8: Patients treated in adherence with the ESC guidelines. Guideline adherence changed from baseline to the 12-months FUP: In the age group 18-61adherence improved from 32% to 46%, in the age group >61 from 31% to 53% and in patients living in rural areas from 22% to 50%. In patients living in the city there was a deterioration from 64% to 50%.

3.2 Outcome and Prognosis

3.2.1 Rehospitalization and Survival

I evaluated the relation between clinical features/risk factors and the outcome by means of mortality (in one year) and rehospitalization (in the previous 6 months).

3.2.1.1 Rehospitalization in various Subgroups

Overall, the occurrence of "rehospitalization" has been registered 17 times in the previous 6 months, but some patients have been rehospitalized more than once (1-3 times per patient). 13 out of 66 patients have been rehospitalized at least once (20%). In the analysis, I subdivided between "rehospitalized" (n=13) and "non-rehospitalized" (n=53) patients.

The reason for hospitalization was also recorded: Out of 17 events of hospitalization, HF was the reason 11 times (65%), twice renal dysfunction was responsible (12%), once the cause was cardiac but non HF, once vascular, once non-cardiovascular and once the cause was unknown (6%, respectively).

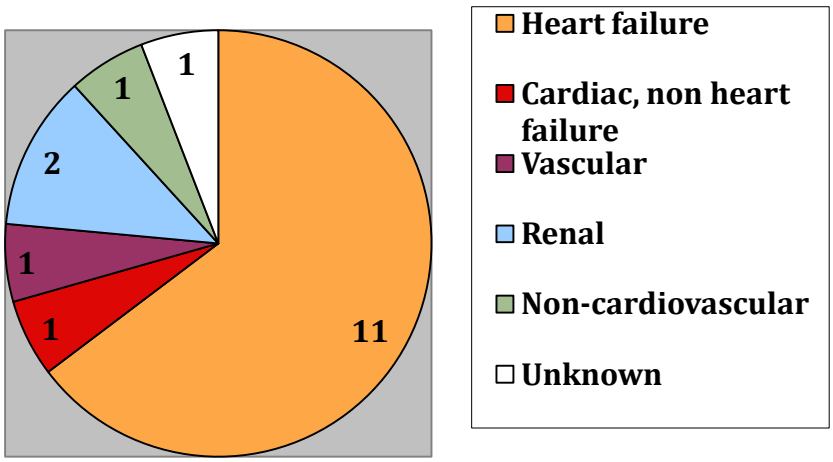


Fig. 9: Causes for rehospitalizations within the previous 6 months. n=13; the patients have been rehospitalized 1-3 times (=17 rehospitalizations overall).

3.2.1.1.1 Ischemic Heart Failure (vs. Non-ischemic)

This parameter was available for 11 rehospitalized patients and for 51 non-rehospitalized patients.

5 (46%) out of 11 patients rehospitalized in the previous 6 months were suffering from ischemic heart failure. In the group without any rehospitalization, 20 out of 51 (39%) had ischemic HF.

3.2.1.1.2 Ejection Fraction <35% (vs. ≥35%)

This parameter was available for 11 rehospitalized patients and for 50 non-rehospitalized patients.

8 (73%) patients out of 11 in the rehospitalized group had an ejection fraction <35%. Out of 50 non-rehospitalized patients, 23 (46%) had an EF <35.

3.2.1.1.3 NT-pro BNP ≥1199 pg/ml (vs. <1199 pg/ml)

This parameter was available for 13 rehospitalized patients and for 50 non-rehospitalized patients.

1199 pg/ml was the median NT-pro BNP in all patients. Therefore, I subdivided the cohort in patients with NT-pro-BNP at or above the median (≥1199 pg/ml) and below (<1199 pg/ml).

Out of 13 rehospitalized patients, 8 (62%) had an NT-pro BNP value ≥1199. In the non-rehospitalized patients, 23 (46%) out of 50 had an NT-pro BNP above the median.

3.2.1.1.4 Diabetes (vs. no Diabetes)

This parameter was available for 12 rehospitalized patients and for 52 non-rehospitalized patients.

In the rehospitalized group, 3 (25%) out of 12 patients were suffering from diabetes. 1 patient had diabetes, but his therapy comprised only dietary control. 1 patient had oral antidiabetic medication and 1 had insulin-dependent diabetes.

In the non-rehospitalized patients, 15 out of 52 (29%) had diabetes. 3 out of these 15 had dietary control, 10 patients had oral antidiabetics, 1 was insulin-dependent and anti-diabetic therapy was unknown in 1 patient.

3.2.1.1.5 Body Mass Index >25 (vs. ≤25)

This parameter was available for 12 rehospitalized patients and for 53 non-rehospitalized patients.

In the rehospitalized patients, 3 (25%) out of 12 had a body mass index >25 compared to 39 (74%) out of 53 non-rehospitalized patients with a BMI >25.

Noteably, 74% of all chronic heart failure patients had a BMI above 25.

3.2.1.1.6 Smoking (vs. non-Smoking)

This parameter was available for all 13 rehospitalized patients and for all 53 non-rehospitalized patients.

By definition, "smoking" includes patients with previous smoking, who have now stopped and patients currently smoking. "Non-smoking" means, that patients have never been smoking regularly.

10 (77%) out of 13 rehospitalized patients have been smoking or are currently smoking. In the non-rehospitalized patients 30 (44%) out of 53 have a positive smoking anamnesis.

3.2.1.1.7 Old Age (>61 vs. 18-61)

This parameter was available in all rehospitalized (n=13) as well as in all non-rehospitalized (n=53) patients.

61 years was the median age in all 66 CHF patients.

In the rehospitalized group, 9 (69%) out of 13 were aged >61 compared to 26 (49%) out of 53 in the non-rehospitalized group.

Figure 10 summarizes the most relevant findings of this analysis.

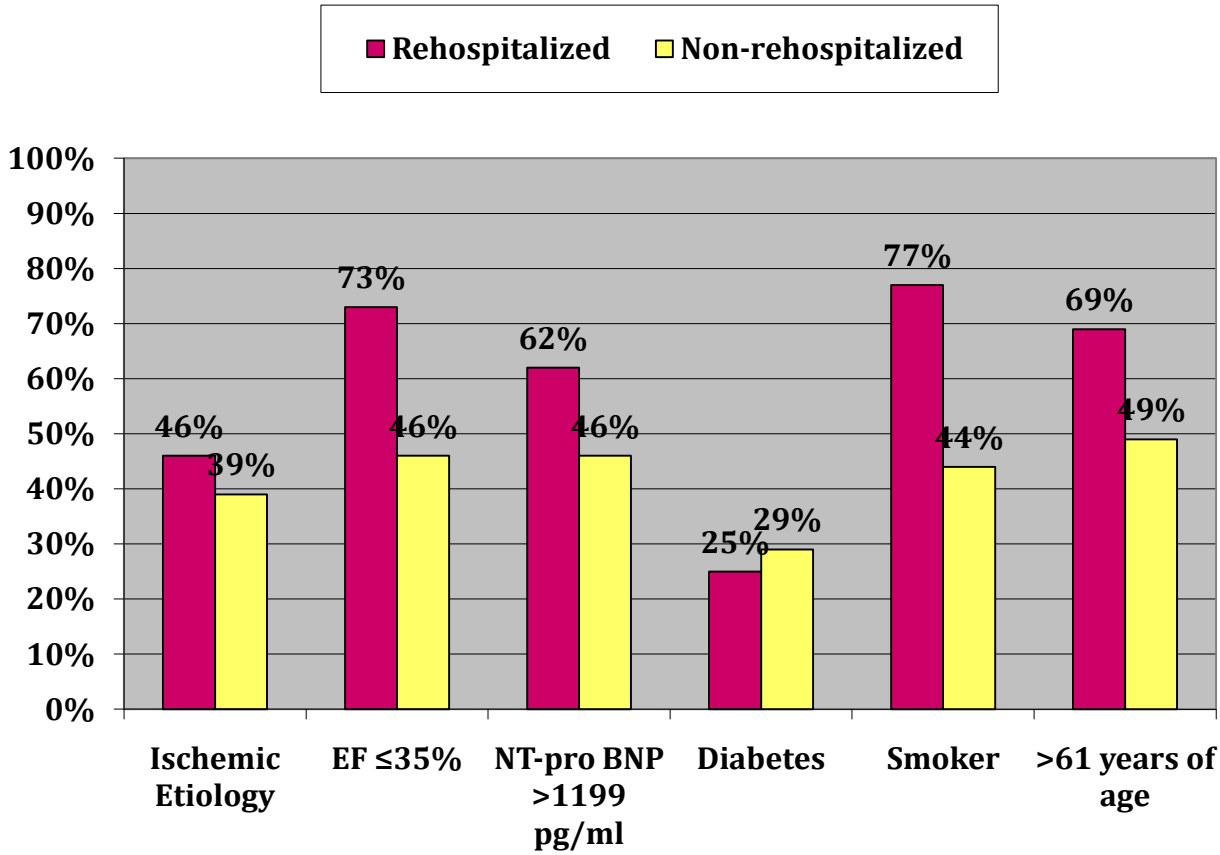


Fig. 10: CHF patients with features associated with poor prognosis. In the rehospitalized group, there are more patients with ischemic etiology, EF <35%, NT-pro BNP ≥1199 pg/ml, current or previous smoking and >61 years of age compared to the non-rehospitalized. Interestingly, only 25% of the rehospitalized patients were suffering from diabetes, but 29% of the non-rehospitalized.

3.2.1.2 Survival

Out of all 66 patients, 4 (6%) did not survive for 1 year. The cause of death was unknown in 1 of these 4 patients; heart failure induced death in the other 3 patients. The mode of death was known in all 4 patients; death occurred suddenly in 2 and non-suddenly in the other 2 patients.

Heart failure was ischemic in 2 and non-ischemic in the other 2 patients, who did not survive. The ejection fraction was <35% in 2 patients; the other 2 had an ejection fraction ≥35%. 3 out of 4 patients had an NT-pro BNP level above the median (1199 pg/ml) and in 1 patient, this value was unknown. The BMI accounted for >25 in 3 out of 4 patients; 1 patient had a body mass index ≤25.

2 out of 4 patients, who died within 1 year, were suffering from diabetes (type 2). 1 of them was insulin-dependent and 1 was prescribed oral antidiabetic medication.

2 out of 4 patients have been smoking previously, but had already stopped smoking at baseline. The other 2 patients have never been smoking.

In the non-survivors, 3 out of 4 were older than 61 years and 1 was aged between 18 and 61.

Figure 11 summarizes these findings in the subgroups.

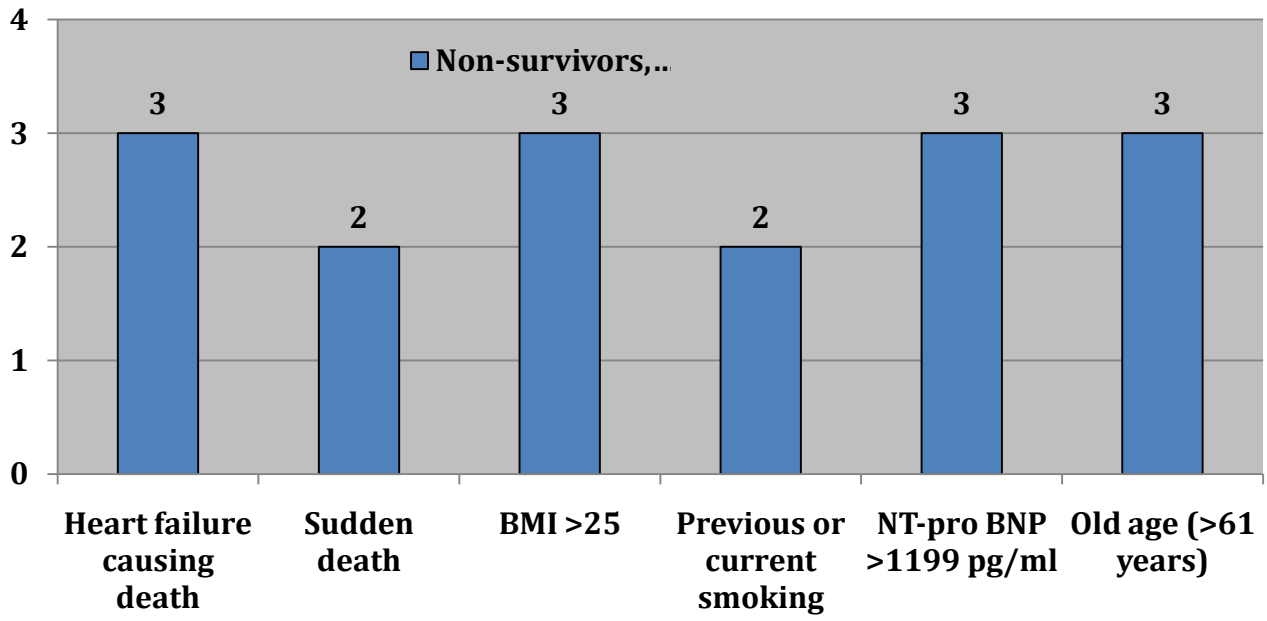


Fig. 11: Clinical features in the 4 non-survivors.

3.2.2 Changes in the NYHA-class from Baseline to the 12 months-Follow up

At baseline information was available in 64 patients, after 12 month in 63 patients. Analysis of NYHA-class changes: n=61.

At baseline, there were 8 (13%) out of 64 patients in NYHA-functional class I. 38 (59%) were classified NYHA II, 13 (20%) NYHA III and 5 patients (8%) NYHA IV.

After 12 months, 7 (11%) out of 63 patients were in NYHA I, 27 (43%) in NYHA II, 26 (42%) in NYHA III and 3 patients (5%) were staged NYHA IV.

23 (38%) out of 61 patients deteriorated to a higher NYHA-functional class from baseline to the 12-months FUP. The other 38 (62%) patients either remained in the same stage (n=29) or they even improved (n=9).

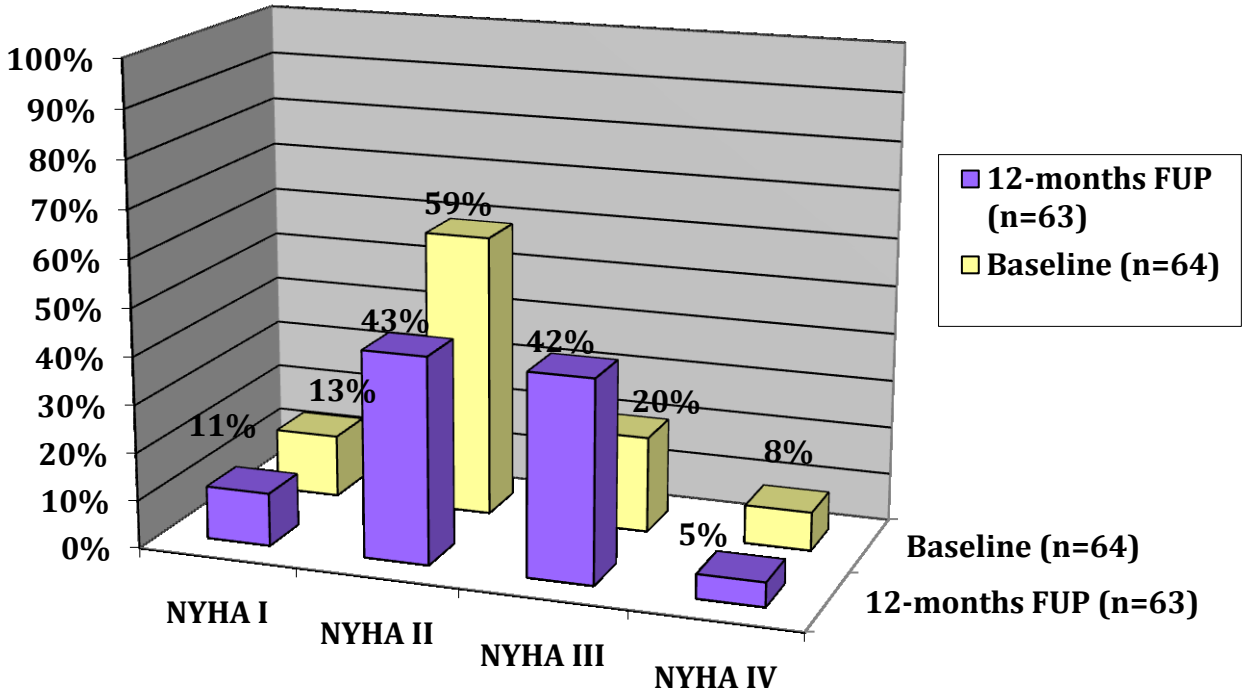


Fig. 12: Patients in NYHA-functional classes I-IV. At baseline and after 12 months, respectively.

3.3 Chemistry – Pathologic Laboratory Parameters in Heart Failure

I used the standard values from the university clinic-laboratory of Graz:

- Anemia is defined by a hemoglobin (hb)-value <12 g/dl in women and <13 g/dl in men.
- A pathologic creatinine-value is defined >1 mg/dl in women and >1.2 mg/dl in men.
- Urea is defined as pathologically by a value >45 mg/dl in women and men.
- The sodium-value value <135 mmol/l is pathologically low in women and men.

3.3.1 Hemoglobin

The hemoglobin was available in 63 out of 66 patients. Subroups: The parameter was available in 3 out of 4 non-survivors and in all 13 rehospitalized patients.

5 (8%) out of 63 patients had a hemoglobin value below normal.

In the non-survivors, 1 out of 4 patients was anemic at baseline, 2 had a normal hemoglobin-values and the hb was unknown in the fourth patient.

In the rehospitalized group, 1 (8%) out of 13 was anemic.

3.3.2 Creatinine

Creatinine was available in 63 out of 66 patients. Subroups: The parameter was available in 3 out of 4 non-survivors and in all 13 rehospitalized patients.

29 (46%) out of 63 patients had a pathologically increased creatinine-level.

1 out of 4 patients who did not survive, had an increased creatinine; 2 had a normal serum-creatinine and the value was unknown in 1 patient.

In the rehospitalized patients, 6 (46%) out of 13 had a creatinine above the norm.

3.3.3 Urea

The urea-level was available in 62 out of 66 patients. Subroups: The parameter was available in 3 out of 4 non-survivors and in 11 out of 13 rehospitalized patients.

30 (48%) out of 62 patients had a urea value >45 mg/dl.

In the 4 non-survivors, there were 2 patients with an increased urea-level, 1 patient with a normal urea-level and 1 patient with an unknown urea-level.

5 (45%) rehospitalized patients out of 11 had a pathologically high serum-urea.

3.3.4 Sodium

Sodium was available in 63 out of 66 patients. Subroups: The parameter was available in 3 out of 4 non-survivors and in all 13 rehospitalized patients.

9 patients (14%) out of 63 had a pathologically reduced serum-sodium.

1 out of the 4 patients, who did not survive, had a sodium-level below the norm, 2 had normal values and the value was unknown in the fourth patient.

The sodium-level was <135 mmol/l in 2 (15%) out of 13 rehospitalized patients.

Figure 13 summarizes these findings.

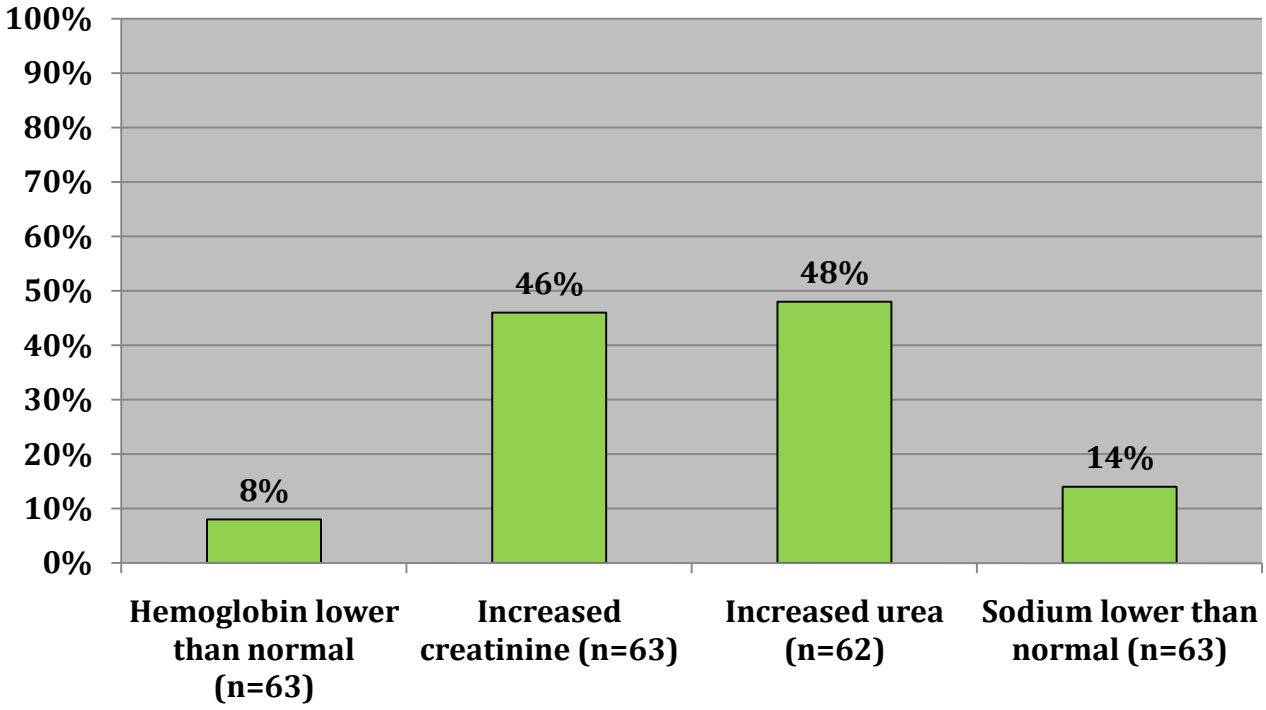


Fig. 13: Anemic CHF patients (hemoglobin <12 g/dl in women and <13 g/dl in men, n=63); patients with an increased serum creatinine (>1 mg/dl in women and >1.2 mg/dl in men, n=63); patients with a pathologically high urea-level (>45 mg/dl, n=62); patients with decreased sodium levels (<135 mmol/l, n=63).

3.4 Gender Medicine and Heart Failure – Differences in Treatment and Prognosis between Women and Men

3.4.1 Risk Factors

Overall, there were 15 female and 51 male patients. Information about risk factors was not available for all patients.

Smoking-status: women: n=15, men: n=51; information about diabetes: women: n=13, men: n=51; BMI: women: n=15, men: n=51; NT-proBNP: women: n=15, men: n=48.

In women 9 (60%) out of 15 have been smoking previously or are currently smoking compared to 31 (61%) out of 51 men.

2 (15%) out of 13 women and 16 (31%) out of 51 men were suffering from diabetes.

10 (67%) out of 15 women had a body mass index >25 compared to 38 (76%) out of 51 men.

5 (33%) out of 15 women and 26 (54%) out of 48 men had an NT-pro BNP value >1199 pg/ml.

Figure 14 summarizes these findings

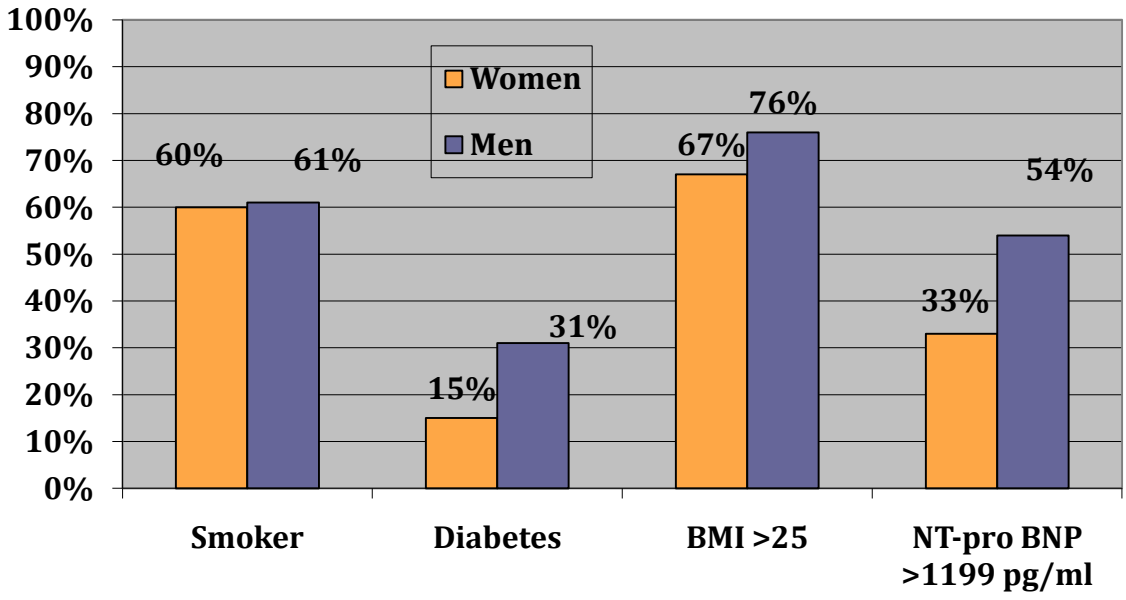


Fig. 14: Differences between women and men in the prevalence of cardiovascular risk factors: Previous or current smoking, diabetes, body mass index >25 and an NT-pro BNP value above the median.

3.4.2 Therapy

Guideline adherence:

This parameter was available in 14 out of 15 women and in 46 out of 51 men.

The guideline-adherence as defined above (p. 34) was given in 5 (36%) out of 14 women at baseline compared to 14 (30%) out of 46 men. After 12 months, 10 (71%) out of 14 women were treated in adherence with the guidelines compared to 20 (43%) out of 46 male patients.

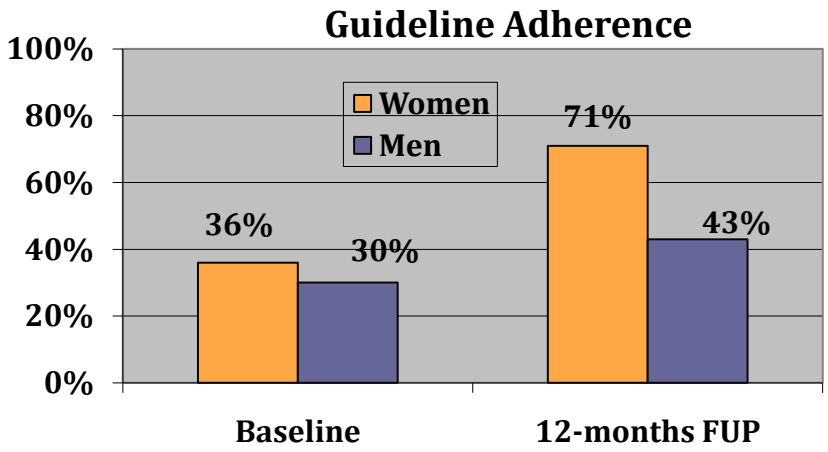


Fig. 15: Women and men with chronic heart failure treated in adherence with the ESC-guidelines.

3.4.3 Prognosis

The four non-survivors were all male.

4 (27%) out of 15 women have been rehospitalized within the previous 6 months compared to 9 (17%) out of 51 men.

NYHA-functional classification:

Information about the NYHA-functional class was available for all 15 female patients both at baseline and after 12 months compared to 49 men at baseline and 48 after 12 months. Further analysis of NYHA-functional class changes is based on 14 women and 47 men.

Female patients:

At baseline, 1 (7%) out of 15 women was in NYHA-class I, 9 (60%) were staged NYHA II, 3 (20%) were in NYHA-class III and 2 (13%) were in NYHA-class IV. After 12 months, 1 (7%) woman out of 15 was in NYHA-class I, 2 (13%) were in NYHA II, 9 (60%) in NYHA III and 3 (20%) were staged NYHA IV.

Male patients:

At baseline, 7 (14%) out of 49 men were in NYHA I, 29 (59%) NYHA II, 10 (20%) were in NYHA III and 3 (6%) were in NYHA IV. At the 12 months-follow up, there were 6 (13%) out of 48 in NYHA I, 25 (52%) in NYHA II, 17 (35%) in NYHA III and no male patients in NYHA IV.

Deterioration to a higher NYHA-classification from baseline to 1 year after happened in 7 (47%) out of 15 women and in 16 (34%) out of 47 men.

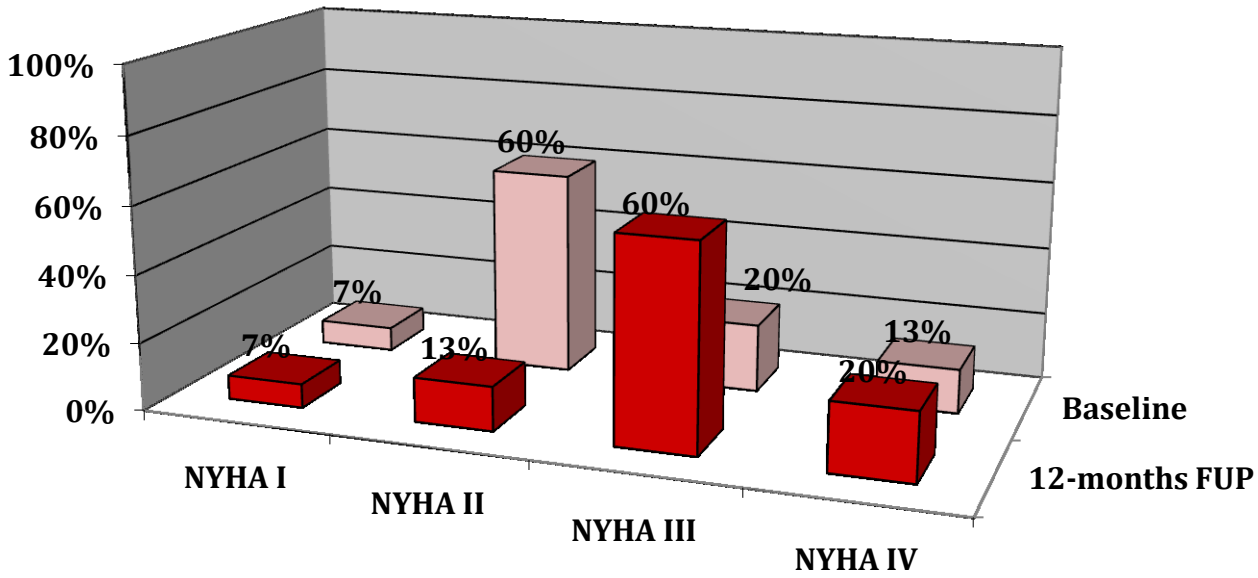


Fig. 16: Female patients in NYHA-functional classes I-IV. At baseline and after 12 months, respectively.

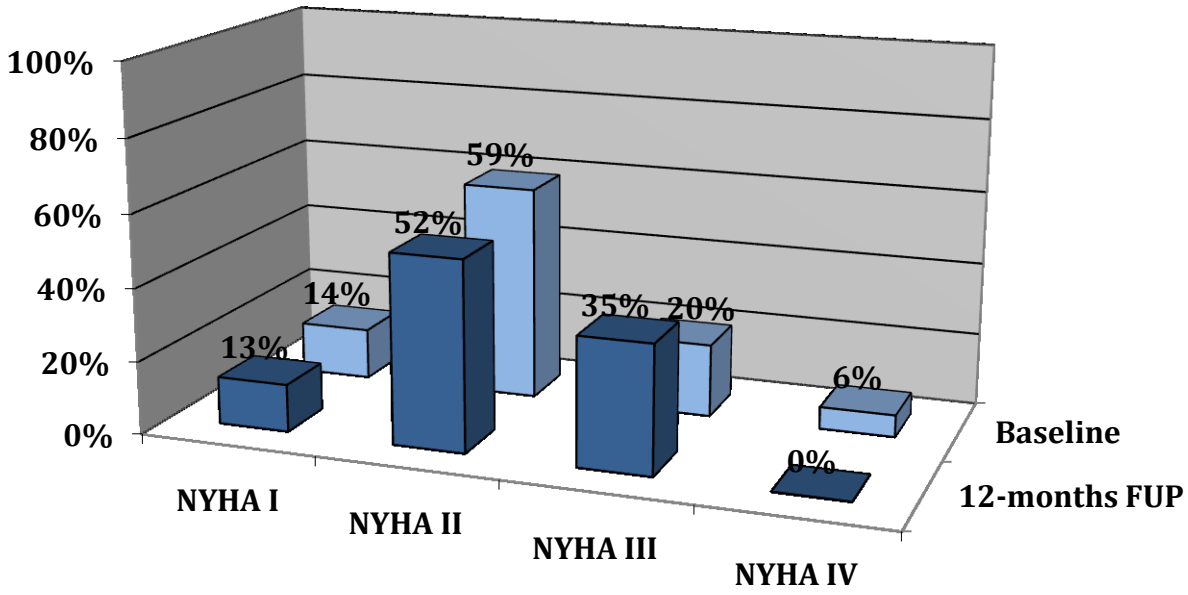


Fig. 17: Male patients in NYHA-functional classes I-IV. At baseline and after 12 months, respectively.

4 Discussion

Although only 66 patients are the basis of this master thesis, it is the largest group of patients with chronic heart failure taking part in the EuroHeart Failure survey – pilot phase in Austria.

4.1 Therapy and Guideline Adherence

4.1.1 Prescription of Beta Blockers, ACEIs and Aldosterone Antagonists

Although ACEI use for heart failure treatment has been established earlier than β-blocker use, my findings suggest, that β-blockers are used more frequently nowadays [19, 20]. It has been reported, that vasoconstriction is in large part responsible for hypertension (ACEI use) and also, that β-blocker use in heart failure is associated with lower mortality [21, 22]. According to the ESC-guidelines, both of these drugs should be used in all heart failure patients (NYHA classes I-IV). Garg et al have shown, that generalists are nowadays less likely to use ACEIs than specialists, also highlighting the frequent β-blocker prescription [23].
Moreover, in consideration of ARBs as an alternative for ACEIs, the percentage of ACEI or/and ARB prescription (84% at baseline and 92% after 12 months) still drags behind β-blocker use (91% at baseline and 95% at the 12 months-FUP).

The prescription rate of aldosterone antagonists in my cohort was relatively high with 65% after 12 months. In other studies, the prescription has been reported around 13% [24, 25]. It can only be speculated why this is the case. A possible explanation would be, that the majority of patients reported here are managed by the university heart failure clinic Graz together with courageous family doctors willing to treat patients at high level of evidence.

4.1.2 Guideline Adherence at Baseline and after 12 Months

The percentage of patients treated conform to the guidelines is 32% at baseline and 50% after 12 months. The average guideline adherence is quite low with 40%; at least with all the required drugs put together (ACEI/ARB, β-blocker, spironolactone). In comparison to other studies on pharmacological heart failure treatment, the guideline adherence is acceptable concerning ACEIs and β-blockers, however: ACEI/ARB prescription has been reported with 54,3% (ADHERE-registry) and 84% (Lainchbury et

al); in the patients in Graz, the average prescription was 88%. Previous data show that β-blockers have been prescribed in 52,4% (ADHERE) and in 65% (Lainchbury), whereas the average prescription rate was 93% in Graz [24, 25].

The prescription of aldosterone antagonists in Graz is high compared to other data, but considering, that all patients in NYHA-classes III and IV should have an aldosterone antagonist, the prescription is still too low.

Patients living in the city of Graz were treated with much better guideline adherence than those living in rural areas at baseline. Surprisingly, guideline adherence deteriorated in the "city"-group from baseline to after one year, whereas all other subgroups were treated with better adherence at the 12 months-FUP. For me it is completely unclear why this is the case.

4.2 Outcome

Mortality and hospital readmission:

The prognosis of the CHF patients in Graz in general is good: The one-year mortality rate is 6%, while other studies report annual mortality rates of 10%-50% [26, 27].

The annual rehospitalization rate in CHF is normally around 30% [28]. In Graz, 20% of the patients have been rehospitalized within 6 months, so there may be room for improvement.

The readmission is a good outcome-parameter according to Costanzo et al, who found, that time to further rehospitalization and death decreases dramatically the more prior hospitalization there have been [29]. In the rehospitalized patients, it was obvious, that heart failure was the main cause for rehospitalization compared to other co-morbidities; it was the reason for 11 out of 17 hospital readmissions.

A cornerstone in preventing heart failure hospitalizations is optimization of heart failure treatment. Therefore, it is good to see that at least in rural patients, guideline adherence improved over the 12 months period. On the other hand it would be interesting to know the reasons for deterioration in the guideline adherence in urban patients as there is a lot of improvement possible.

NYHA-functional classification:

Increasing NYHA-functional classification means increase of risk and worsening of prognosis. Pocock et al found, that the hazard was increased by 32% and 54% in NYHA classes III and IV, respectively, in comparison to NYHA class II [30].

In the patients from Graz, most remained in the baseline-NYHA class after 12 months. 23 deteriorated and only 9 patients improved. This suggests, that there is limited room to improve the prognosis of heart failure, because despite of good treatment, it is still a disease of the elderly with old age contributing considerably to clinical deterioration.

However, one has to be cautious on NYHA-classes. Zugck et al found, for instance, that functional capacity varies considerably in heart failure, even over short periods of time [31].

4.3 Gender Aspects

4.3.1 Guideline Adherence in Women and Men

Women were treated in better adherence with the guidelines at baseline (36% versus 30% in men) and after 12 months (71% versus 43% in men). It remains unclear, why the guideline adherence rather increases in women than in men. Maybe, women have been treated more dedicatedly, because their functional capacity (NYHA-class) is worse compared to male patients.

4.3.2 Readmission, Mortality and NYHA-classification

All the non-survivors in Graz were male. This can either be explained by male gender alone or by the higher prevalence of risk factors in men (e.g. diabetes, smoking) or by the simple fact men by far outnumbered women in this study. Better guideline adherence in women could also be an explanation.

Although survival is better in women, the readmission rate was higher (27% compared to 17% in male patients) and moreover, women were more likely do deteriorate in the NYHA-class: The average NYHA-class in female patients at baseline was 2,39 whereas 2,16 in men and after 12 months, the average NYHA-class in female patients was 2,93 and in male patients 2,22.

One the one hand, survival is better in women, but the higher hospital readmission rate and worsening of functional capacity suggest a more unstable disease in women compared to men.

According to a study on gender differences in heart failure patients, women survive longer after the onset of heart failure, but they tend to be older than men when diagnosed with heart failure and they experience a lower overall quality of life [32].
In fact, previous findings have shown, that the outcome in women with heart failure is generally better than in men [33].

5 Conclusion

Outcome in chronic heart failure at the university clinical center Graz is better than reported in the literature (94% survival). However, guideline adherence in these patients leaves room for improvement. Many patients deteriorated regarding the NYHA-functional classification within one year. This shows, that heart failure is a progressive disease with limited chance for healing.

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