Heart failure disease management program, its contribution to established pharmacotherapy and long-term prognosis in real clinical practice – retrospective data analysis

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Background and Aims. The prognosis of patients with heart failure (HF) is still generally unfavorable. HF with reduced ejection fraction (HFrEF) patients reach target medication doses in very low percentages in daily clinical practice. HF disease management programs (DMP), including nurse and telemedicine support that facilitate achieving target medication doses, may improve the unfavorable prognosis.

Methods. We retrospectively analyzed the data of 738 patients with HFrEF who were followed in a single HF center during the years 1975–2011, for 6.4 (median) years. DMP, nurse and telemedicine support is established at this center.

Results. The group achieved left ventricle (LV) recovery after the HF treatment. The median LV ejection fraction improved from 25.0% at baseline to 50.0% at the time of the latest data collection. The proportion of NYHA II, III and IV classes decreased from 27.6%, 30.2% and 29.7% to 26.6%, 7.2% and 0.1%, respectively while the proportion of NYHA class I increased from 12.5% to 66.1%. Median NT-proBNP decreased from 975.0 to 324.0 pg/mL. The survival of the patient group was favorable; 79.7% survived 18.1 years after diagnosis of HF. A high percentage of the patients received recommended target or higher than target doses of angiotensin-converting enzyme inhibitors (82.0%) and beta-blockers (78.1%).

Conclusion. The established pharmacotherapy resulted from an effective DMP and this contributed to the favorable prognosis.

Key words: disease management program, heart failure, long term prognosis, pharmacotherapy dose

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INTRODUCTION

Congestive heart failure (CHF) is one of the most serious medical and socio-economic problems in the western world. It afflicts 1–2% of the population with a significant increase in prevalence in older age groups. According to the 2016 ESC Guidelines, an aging population along with the success of acute cardiovascular medicine leads to an increase in the prevalence of heart failure (HF)[1]. The prognosis of HF patients, despite significant advances in care in recent decades, is still unfavorable. Up to half of the patients die within 5 years after CHF diagnosis[1]. In addition to the serious prognosis, morbidity is also an important issue for patients with HF. The course of the disease is accompanied by frequent re-hospitalizations for decompensation of HF which is associated with a significant worsening of the prognosis[2].

Unfortunately, we know from clinical practice and the results of a number of registries that only a small proportion of patients are receiving the recommended HF disease modifying medication doses[3-5]. This unsatisfactory situation persists, despite the fact that the beneficial effect of treatment increases with dose[6], especially so for beta-blockers[7].

It has been repeatedly reported that a well-established Disease Management Program (DMP) for HF has significant potential to improve the prognosis of patients[8-11]. This is due to early diagnosis of HF, adequate patient education and the setting up of therapy according to Guidelines, including up-titration of pharmacotherapy with mortality benefit to target doses, if clinically feasible[8-11].

In this paper, we describe a group of patients with HF with reduced ejection fraction (HFrEF) who reached left ventricle (LV) recovery, long-term stabilization and showed good prognosis. We mainly analyzed the established pharmacotherapy with mortality benefit in this patient group.

Table 1. Descriptive statistics and statistical comparison of obtained data.

Parameter	Baseline characteristics	The latest data collection characteristics
Age (median; 1st-; 3rd-quartile) [years]	55.0; 46.2; 64.2	62.7; 53.4; 71.4
Follow-up time (median; 1st-; 3rd-quartile) [years]	6.4; 4.3; 9.8	
Male [%]	70.2	
Female [%]	29.8	
HF history - ICMP [%]	34.1	
HF history - NICMP [%]	65.9	
AH history [%]	52.2	
DM history [%]	22.0	
COPD history [%]	5.7	
SVT history (atrial fibrillation or atrial flutter) [%]	33.1	
NYHA:	***	***
NYHA I [%]	12.5	66.1
NYHA II [%]	27.6	26.6
NYHA III [%]	30.2	7.2
NYHA IV [%]	29.7	0.1
Mitral regurgitation:	***	***
Mitral regurgitation 0 [%]	27.0	55.4
Mitral regurgitation 1 [%]	26.5	34.4
Mitral regurgitation 2 [%]	21.2	8.1
Mitral regurgitation 3 [%]	24.6	1.9
Mitral regurgitation 4 [%]	0.6	0.1
LVEF (median; 1st-; 3rd-quartile) [%]	25.0***; 20.0; 35.0	50.0***; 40.0; 60.0
LVEDD (median; 1st-; 3rd-quartile) [mm]	62.0***; 56.0; 67.9	56.0***; 51.0; 62.0
PASP (median; 1st-; 3rd-quartile) [mm Hg]	39.0***; 31.0; 49.0	31.0***; 26.0; 37.0
BNP (median; 1st-; 3rd-quartile) [pg/mL]	324.0***; 90.0; 760.0	83.0***; 32.8; 183.3
NT-pBNP (median; 1st-; 3rd-quartile) [pg/mL]	975.0***; 331.8; 2271.5	324.0***; 120.0; 802.0
Systolic blood pressure (median; 1st-; 3rd-quartile) [mm Hg]	NA	113.0; 100.0; 130.0
Diastolic blood pressure (median; 1st-; 3rd-quartile) [mm Hg]	NA	69.0; 60.0; 78.0
Heart rate (median; 1st-; 3rd-quartile) [L/min]	NA	66.0; 60.0; 72.0
Creatinine (median; 1st-; 3rd-quartile) [µmol/L]	NA	94.0; 77.8; 114.0
GFR (median; 1st-; 3rd-quartile) [mL/(min 1.73 m²)]	NA	67.0; 54.0; 83.8
ICD [%]	NA	26.2
CRT [%]	NA	11.8

*** indicates statistically significant difference at $P<0.001$. NA means not-available.

MATERIALS AND METHODS

Analysis Setting

We analyzed a group of 738 patients with HFrEF who were followed at Heart Function Clinics, St. Paul's Hospital, Vancouver, Canada during the years 1975–2011.

A sophisticated DMP for HF with the significant involvement of nurses and telemedicine technologies is well established in the institution. Specialized HF nurses are involved in the education of patients, telephone consultations, telephone follow-ups, medication changes and up-titration according to the protocols. The nurses also do physical examination of patients and are involved in coordinating care.

The analyzed group of patients was transferred to the "maintenance" clinics according to the institutional protocol. These patients showed statistically significant improvement in NYHA class, degree of mitral regurgitation, LV ejection fraction (LVEF), left ventricular end diastolic diameter (LVEDD), pulmonary artery systolic pressure (PASP) (all four items classified by echocardiography), and BNP and NT-pBNP levels after HF treatment and clinical follow-up (see Table 1).

We retrospectively analyzed this group of "recovered" HF patients, especially the established pharmacotherapy with mortality benefit and we also assessed the survival of this selected patient group. We compared the data with registry data and HF clinical trial populations.

The retrospective data analysis was approved by the

Table 2. Analysis of HF medical therapy at the time of the latest data collection.

ACEIs	
Total [%]	60.8
Within Total	
Ramipril [%]	88.9
Perindopril [%]	5.6
Quinapril [%]	2.7
Trandolapril [%]	0.5
Enalapril [%]	1.3
Lisinopril [%]	0.4
Accupril [%]	0.4
Monopril [%]	0.2
ARBs	
Total [%]	28.1
Within Total	
Candesartan [%]	69.6
Telmisartan [%]	7.2
Losartan [%]	11.1
Valsartan [%]	12.1
Beta-blockers	
Total [%]	86.4
Within Total	
Carvedilol [%]	45.1
Bisoprolol [%]	38.1
Metoprolol Succinate [%]	13.3
Metoprolol Tartarate [%]	3.2
Atenolol [%]	0.3
MRAs	
Total [%]	25.3
Within Total	
Spironolactone [%]	96.3
Eplerenone [%]	3.7

ethics committee of the first author's institution (reference number 42/18).

Statistical Analysis

Descriptive statistics were used on the patient baseline data and at time of the latest patient assessment. Patient data were obtained from the medical records of the clinics. Patients selected for the analysis were part of the "maintenance" clinics, where those with HF and long-term stabilization and improved clinical condition were transferred to. The primary data analysis was a description of the selected patient population. The pharmacotherapy at the latest data collection was also analyzed. The percentage of patients in selected drug groups (angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), beta-blockers) was analyzed. The percentage of each subgroup of medication was also assessed. We investigated the percentage of patients adjusted to target or even supramaximal doses of individual drugs and drug groups.

All interval data were first tested for normality using the Shapiro-Wilk test and all data failed ($P<0.001$). Thus, they are described by medians, 1st- and 3rd-quartiles. To evaluate statistically significant difference between paired baseline and the latest interval-type data, the Wilcoxon signed rank test was used, since differences in the paired data were not normally distributed ($P<0.05$). This test was also used for finding statistically significant differences for ordinal data (*New York Heart Association* (NYHA) and mitral regurgitation classes). The Kaplan-Meier survival analysis with censored data was performed based on follow-up times determined from dates of the first (baseline) and the latest NYHA class determination. Excel (Microsoft) and SigmaPlot (Systat) were used for evaluation of the descriptive statistics and statistical testing.

RESULTS

Patients Characteristics

The group consisted of 738 HFrEF patients, median age 62.7 years at the date of latest data collection, of whom 70.2% were male and 29.8% female (see Table 1). The median patient follow-up time since diagnosis was 6.4 years with a minimum of 0.3 years and a maximum of 35.0 years. Throughout the observation period, the patients were hospitalized on average for 1.2 times for decompensated HF. Of these, 21.5% of patients were not hospitalized at all and 53.9% of patients only once. Etiologically, 65.9% of patients had non-ischemic cardiomyopathy (NICMP) and 34.1% ischemic cardiomyopathy (ICMP).

Patient comorbidities, such as arterial hypertension (AH), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD) and supraventricular tachycardia (SVT; atrial fibrillation or atrial flutter) are shown in Table 1. The table also shows NYHA classes (I, II, III, IV), mitral regurgitation classes (0, 1, 2, 3, 4), LV ejection fraction (LVEF; during follow-up, median of the lowest LVEF was 22.0%), left ventricular end diastolic diameter (LVEDD), pulmonary artery systolic pressure (PASP), BNP and NT-pBNP levels of the patients at baseline.

Therapy

Patients were adjusted to maximum doses of HF medication according to their tolerance, based on Guidelines recommendation. HF medication analysis was performed from the latest data collection – in the phase of stabilized disease. The percentage of patients treated with particular drug groups at the time of analysis as well as of each drug within a group is shown in Table 2.

75.3% of patients on ACEIs were receiving ramipril target dose 10 mg daily or higher, target dose of perindopril of 8 mg per day and more had 3.3% of the ACEI patients, 2.5% of ACEI patients had quinapril target dose of 20 mg per day and more, target dose of trandolapril of 4 mg per day for 0.2% of ACEI patients, target dose of enalapril of 20 mg per day and more had 0.7% of ACEI patients. Other ACEIs than recommended in the Guidelines were observed in the medication (see Table 2), as class effect is assumed and local habits must be taken into account.

As for ARBs, 23.2% of ARB patients had a target dose

of 32 mg of candesartan per day or higher. 3.9% of ARB patients were on a dose of telmisartan of 160 mg per day or greater. A target dose of losartan of 150 mg per day or more was taken by 1.0% of ARB patients and a target dose of valsartan of 320 mg daily by 3.9%. ARBs were administered according to Guidelines except for a small number of patients receiving telmisartan, which was again due to local habits.

The most frequently used beta-blocker was carvedilol (see Table 2), as a target dose of 50 mg daily or more in 40.6% of beta-blocker patients. A daily target dose of bisoprolol of 10 mg or more and a metoprolol dose of 200 mg or more had 27.0% and 10.5% of beta-blocker patients, respectively.

In MRA therapy, a spironolactone target dose of 50 mg daily or more was used in only 1.1% of patients on MRA and 50 mg daily or more of eplerenone, was taken by 0.5% of MRA patients.

If we count the percentage of patients who were on the target or higher doses of individual drug groups, we get the results shown Fig. 1. In relation to non-pharmacological treatment (see Table 1), 26.2% of patients had an implantable cardioverter-defibrilator (ICD) and 11.8% underwent cardiac resynchronization therapy (CRT).

Evaluation of Prognostic Parameters

Values for parameters obtained at the time of the latest data collection, when the disease was stabilized, reverse remodeling of the left ventricle (LV) was achieved and pharmacotherapy established, are summarized in Table 1.

Mortality

The results showed that 79.7% of the stabilized patient population survived 18.1 years after diagnosis was established (see Fig. 2).

Fig. 1. Percentage of patients on target and higher than target dose of medication in each medication group (ACEIs, beta-blockers, ARBs, MRAs) at the time of the latest data collection.

Fig. 2. Kaplan-Meier survival curve.

DISCUSSION

We analyzed a group of HFrEF patients with improved and stabilized clinical condition and objectively accompanied by LV reversal remodeling (improvement in LVEF, decrease in LVEDD, degree of mitral regurgitation and pulmonary hypertension). Also improvement in NYHA class and decrease in natriuretic peptide levels was documented. All these changes were statistically significant (Table 1).

In our group of patients, there were mostly patients with NICMP (65.9%), which is different from the standard population of HF patients and registry data where a higher proportion of patients with ICMP is found[5]. The patient population was rather young, with a median of 62.7 (mean 61.4) years at the latest data collection. For example, in the study IMPROVE HF, the average age was 71 years[12], in BIOSTAT-CHF the average age was 68 years[7]. This may be the reason for better co-operation and up-titration of medication compared with elderly patients. Also, the monitored patient population had fewer comorbidities than, e.g., the European Observation Program and the BIOSTAT-CHF study[5,7,13], which may be another reason for better medication up-titration, better co-operation
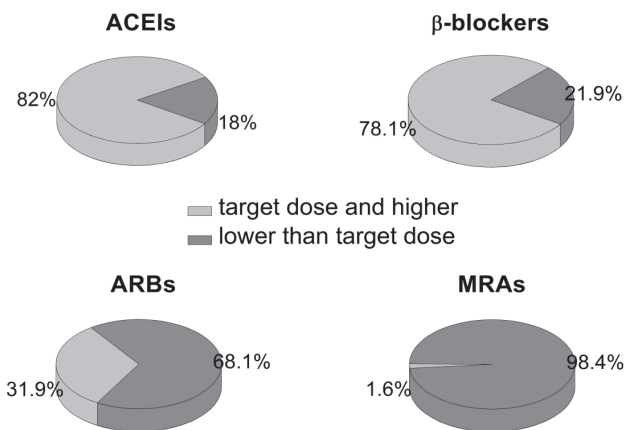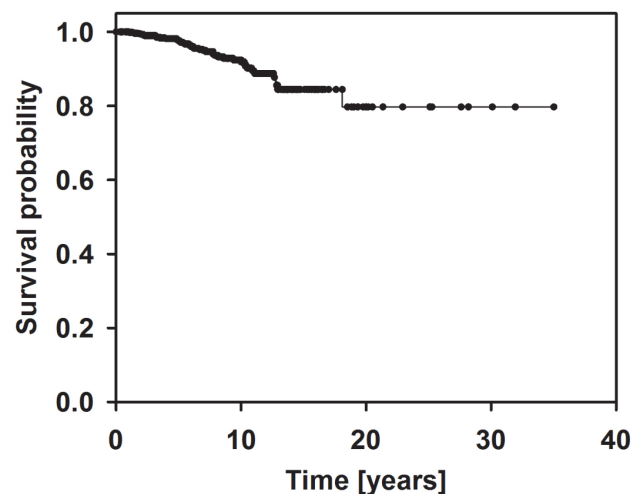
than in older polymorbid patients, and, of course, the reason for better prognosis.

The survival of our patient sample was much better than the general population of HF patients, where mortality is still 40 – 50% within 5 years after the diagnosis[1].

One of the factors in the favorable prognosis of our patients was established pharmacotherapy (Fig. 1). For MRAs, only 1.6% of the patients were on the target or higher dose, however, it should be mentioned that the evaluation was performed at the time of improved LVEF. In addition, data supporting the administration of MRAs appeared for the first time in 1999 when RALES study was published, which, moreover, included only patients in functional NYHA classes III and IV (ref.[14]). In 2011, the results of EMPHASIS-HF study were published, which extended the administration of MRAs to patients in NYHA II functional class[15]. According to the PARADIGM-HF study published in 2014, over 50% of patients had initial MRA treatment[16]. In this context, the low MRA representation in our patients is explainable. The change in treatment habits is also documented by the MERIT-HF initial medication analysis from 1999, where MRAs had

not been monitored at all (and this was not required for inclusion), but 67% of patients had digoxin[17].

With the exception of MRAs, the maximum medication doses in our case were comparable to those of clinical trials, where 49 – 84% of patients had target doses of ACEIs and ARBs and 66 – 80% had target doses of beta-blockers[12]. However, the reality of the common population of patients with HF is different in clinical practice. Comparison with real practice is the European HF registry, where target medication doses were achieved in the following percentages: 29.3% for ACEIs, 24.1% for ARBs, 17.5% for beta-blockers, and 30.5% for MRAs (ref.[5]). According to other observational studies, only 5% of HF patients are at the target dose medication after hospitalization and 15% of HF patients are at the target dose of medication after a follow-up cardiologist visit[4]. However, for example, in the SHIFT study, where 90% of the patients had beta-blockers, the target dose was reached in only in 26% (ref.[3,18]). In particular, the maximal titration of beta-blocker therapy in our patient group is noteworthy[7]. A large percentage of our patients were at target and even supramaximal doses.

Proportional representation of groups of beta-blockers is also interesting. The most commonly used is carvedilol, which accounts for 45.1% from all beta-blockers. The target daily dose of 50 mg and above included 40.6% of patients on beta-blockers. With bisoprolol were treated 38.1% of beta-blockers patients; a target daily dose of 10 mg or more had 27.0% of beta-blocker patients. Metoprolol succinate medicated 13.3% of beta-blockers patients, with a target daily dose of 200 mg and higher in 10.5% of beta-blocker patients. The use of beta-blockers for HF with reduced LVEF has very strong data on mortality reduction and certainly the most robust data in terms of target-specific mortality reduction[6,7,19-22].

As mentioned above, nearly half of the patients treated with beta-blockers in our analysis are on carvedilol. Carvedilol, just like a non-selective ß1, ß2 and α-adrenergic receptor blocker, has a remarkable position among beta-blockers indicated for HF. Instead, ß1 receptors are down-regulated in failing myocardium while the amount of ß2 receptors remains unchanged and the α1 receptors in the failing myocardium are increasing[23]. Also, adrenergic blockade caused by carvedilol, together with an antioxidant effect and increased insulin sensitivity, may play a positive clinical role in the patient improvement[24]. The antioxidant action of carvedilol reduces endothelial dysfunction and has antiapoptotic effect, which also has a favorable clinical impact on the progression of HF (ref.[19]). Combined alpha and beta blockade is more effective in reducing the toxic effect of catecholamines on myocardium and may contribute to a more significant reduction in mortality as clinically demonstrated in the COMET study, which resulted in a higher mortality reduction in HFrEF patients medicating carvedilol *versus* metoprolol[19].

Limiting clinical condition for administration of the maximum dose of beta-blockers is in addition to the induction of hypotension and also an excessive drop in heart rate. In our group, with a high percentage of target beta-blocker doses, the median heart rate was 66.0 1/min.

It is a question whether a group of patients achieving titration of medication to target doses is not primarily different and with primarily better prognosis. In patients who did not succeed in medication up-titration, their overall condition and comorbidities often prevent them from achieving higher doses (hypotension, renal insufficiency, mineral balance disturbances). Thus, in patients who are initially expected to have a better prognosis, therapy is better titrated to maximum and opposite.

On the other hand, there could be also a system error – patients are not up-titrated because of the absence of DMP. Limitations caused by the treating staff (acceptance of the results of clinical studies, knowledge of Guidelines and its transfer to practice, diligent work with the patient, explanation of individual steps, adequate education, co-operation of the whole team, etc.) can influence the situation. The institution at which the data analysis was performed has a very good system of care for HF patients (DMP) with a strong involvement of nurses, telemedicine technologies, protocols for medication up-titration.

Unfortunately, routine clinical practice in countries where DMP is not introduced leads to a significant number of HF patients who do not reach the target dose of medication, or who do not get recommended mediation at all[25]. One of the predictors of lower target doses of HF medication in the BIOSTAT-CHF study was country of inclusion[7]. Lower doses were found in Central and Southern Europe and higher are reported in patients from Scandinavian countries where DMP is common. The introduction of DMP may therefore increase the target beta-blocker dose from 10% to 43% due to frequent nurse control and up-titration therapy[12]. After the introduction of the telemetry titration protocol, 71% of patients achieved the target beta-blocker dose in 8 weeks[12].

It is also necessary to mention the possibility of a higher frequency of LV recovery in patients with recently established non-ischemic dilated cardiomyopathy with potential myocarditis, but this was not determined bioptically or by MRI in this patient group[26,27]. The number of patients with NICMP was significantly higher in our sample than in other population of patients with cardiovascular disease, published studies, where, on the contrary, the ischemic etiology of HF predominates[5,7]. Interestingly, there were only 26.2% of patients with ICD and 11.8% of CRT in our sample. According to the guidelines, it is advisable to indicate CRT-D only after there is no improvement in the status following optimal drug therapy. Indications of ICD in patients with NICMP (65.9% in the analyzed population), especially in the light of recently published data, is considerable[28].

Limitations

The limitation of this study is that it is a retrospective data analysis of patients with no control group. Also, given the relatively long period of time (1975 – 2011), the results are influenced by changes in the diagnosis and treatment of HF.

CONCLUSION

An established HF DMP with involvement of specialized nurses, telemedicine technologies and up-titration medication protocols positively affects a patient´s prognosis. The selected group of HFrEF patients who achieved LV recovery had well-established HF pharmacotherapy achieving target medication doses in high percentage. This was especially evident for beta-blockers. Such a high percentage of HFrEF patients reaching target medication doses is unique in common clinical practice.

Author contributions: ML: data collection, data interpretation, manuscript writing; DL data analysis, statistical analysis, figures; AI and FM: study design; JV and MT: participation in revision of the manuscript.
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