The prognosis and therapeutic management of patients hospitalized for heart failure in 2010–2020

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Aims. We analyzed the mortality risk and its predictors in patients hospitalized for heart failure (HF).
Methods. Patients discharged from hospitalization for acute decompensation of HF in 2010–2020 and younger than 86 years were followed (n=4097). We assessed the incidence and trends of all-cause death, its main predictors, and the pharmacotherapy recommended at discharge from the hospital.
Results. The 30 days all-cause mortality was in discharged patients 3.2%, while 1-year 20.4% and 5-years 55.4%. We observed a modest trend to decreased 1-year mortality risk over time. Any increase of year of hospitalization by one was associated with about 5% lower risk in the fully adjusted model. Regarding predictors of 1-year mortality risk, a positive association was found for age over 65, history of malignancy, and peak brain natriuretic peptide during hospitalization ≥10times higher than normal concentration. In contrast, as protective factors, we identified LDL ≥1.8 mmol/L, treatment with beta-blockers, renin-angiotensin axis blockers, statins, and implanted cardioverter in the same regression model. The ejection fraction category and primary etiology of HF (coronary artery disease vs. others) did not significantly affect the mortality risk in a fully adjusted model.
Conclusions. Despite advances in cardiovascular disease management over the last two decades, the prognosis of patients hospitalized for heart failure remained highly unfavorable.

Key words: cardiac decompensation, hospitalization, mortality risk, pharmacotherapy

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INTRODUCTION

Heart failure (HF) is an ultimate complication of most cardiovascular diseases. From that reason represents a very heterogeneous group of manifestations, with different clinical courses, management as well as prognosis[1]. Patients in whom the progression of chronic heart failure (or acute heart failure as the first manifestation of the disease) has required hospitalization are indeed one the most severe group in terms of the staging of the disease. The prognosis of these patients significantly depends not only on the acute management at the time of hospitalization but even more on the subsequent long-term measures. Fortunately, many clinical trials in the field of heart failure have been conducted over the last 25 years and can now help us determine the proper treatment strategy. To manage HF patients properly, help us also a series of Guidelines, summarizing the most important evidence-based procedures, the most recent ones are from 2021 (ref.[2]). However, the success of any treatment strategy determined the consistency of its implementation to clinical practice, and the reality needs to be verified regularly.

This study aimed to analyze the mortality risk and its development over time in the sample of patients hospitalized for heart failure between 2010 and 2020. Moreover, we determined the prescription of main drugs with a prominent role in the treatment of HF, some comorbidities, and other conditions, as well as their role in individual mortality risk.

METHODS

All procedures performed in this study followed the Good Clinical Practice principles and ethical standards formulated in the 1964 Declaration of Helsinki and its later amendments. The Ethics Committee of the University Hospital in Pilsen approved the study protocols. The data were stored and evaluated under the provisions of the Czech Data Protection Act, a GDPR direction of the European Committee. All subjects signed a written informed consent at admission to the hospital (a baseline point of follow-up analysis).

Design and Study Population

The analysis represents a descriptive cross-sectional survey and prospective cohort study of mortality risk in patients after HF hospitalization. Patients hospitalized in University Hospital Pilsen (on five different departments, dealing with internal diseases) between January 1, 2010,

and September 29, 2020, involved for de-novo worsening of HF requiring acute hospitalization (HF should be formally stated in the discharge summary as the primary cause leading to this hospitalization), without known hospitalization for heart failure in at least previous ten years (the prior worsening of heart failure, requiring only outpatient clinic management was acceptable). A total of 9354 hospitalizations we found in the hospital information system during the period under review, which gave us a set of 5804 patients (3550 hospitalizations occurred in the same individuals as recurrence of HF; in this case, we used the data from the first hospitalization during the study period). From this pool, 1140 were older than 85 years, and we excluded 138 subjects after reviewing their documentation (usually because the HF was not found to be the main cause of their hospitalization). Thus, the initial sample consisted of 4526 subjects.

Data collection

For descriptive analysis, only data contained in the hospital information system were used (usually in discharge reports); no formal examination was done in conjunction with this study. The following information was registered: essential anamnestic circumstances, such as the history of cardiovascular diseases, coronary revascularizations, diabetes mellitus, hypertension, known malignancies, history of smoking, and formally stated etiology of HF. Information about ejection fraction (EF) we derived from echocardiography realized during hospitalization (in the vast majority of patients). If not recognized, we used the most recent echocardiography available, or the ejection fraction formally stated in medical records. Information about atrial fibrillation or flutter we derived from ECG realized during hospitalization, or this diagnosis was formally stated in the discharge summary. Moreover, pharmacotherapy recommended in the discharge report was also registered, including dosage of drugs of particular interest (such as beta-blockers, renin-angiotensin system (RAS) blockers, MRAs, and statins).

Information about essential laboratory examinations (glycemia, serum lipids, creatinine, and natriuretic peptides) we derived from the hospital information system. The central hospital laboratory (Department of Clinical Biochemistry and Hematology, University Hospital Pilsen) is involved in regular quality control of all procedures (instruments, laboratory estimations, etc.). Only standard commercial kits and analytical platforms (namely COBAS 8000 analytical platform, ROCHE Diagnostics, Basel, Switzerland) were used for laboratory estimations.

The vital status of patients was registered up to December 31, 2020, using the National Registry of the Institute of Health Information and Statistics of the Czech Ministry of Health. Death certificates and available documentation in hospital information systems were reviewed and used to specify the cause of death.

Data management

Above all, the sample we categorized from two perspectives. First, we divided it according to the EF category into three typical phenotypes of HF: HFrEF, HF with reduced ejection fraction (i.e., ≤ 40%); HFmrEF, HF with mid-range ejection fraction (i.e., 41–50%); HFpEF, HF with preserved ejection fraction (i.e., >50%). Second, we defined two groups ("CAD-related" and "nonCAD-related") by the presumed leading etiology of HF as follows. All cases with a history of myocardial infarction, myocardial revascularisation, or angiographically proven stenosis of coronary artery ≥ 50% we considered as CAD-related HF. In the remaining part of the sample, we identified patients in whom a diagnosis of dilated cardiomyopathy (CMP), tachycardia-induced CMP, post-inflammatory CMP, or other apparent secondary etiology (for example, anticancer treatment-related CMP, alcohol-induced CMP, etc.) was clearly stated in discharge summary (or we have reached this impression based on a review of the available documentation) – these all categories were considered as nonCAD-related HF. Finally, patients with hypertension who did not fall into any of the categories mentioned above we included in the CAD-related group.

Other comorbidities were defined as follows. Hypertension, if this diagnosis was explicitly mentioned in the discharge summary, or if the patient was treated with antihypertensives beyond those used in the treatment of HF. Diabetes mellitus we defined as highest fasting glucose during hospitalization ≥7 or non-fasting glucose ≥11.1 mmol/L, or Hba1c ≥70 mmol/mol, and/or treatment with antidiabetics, as well as the history of diabetes. Hypercholesterolemia we defined as LDL-cholesterol ≥1.8 mmol/L. Using the highest creatinine value detected during hospitalization, we calculated estimated glomerular filtration (eGFR) by CKD-EPI formula[3], and this value was dichotomized as <60 mL/min. Markedly increased brain natriuretic peptide (BNP) was defined as 10-times higher normal value or above, i.e., BNP ≥1000 or N-terminal BNP ≥3000 ng/L. History of malignancy means that this condition was mentioned anywhere in the available documentation, irrespective of current staging or grading.

As outcomes, we used all-cause death during 30 days, 1st year, and 5 years after the admission to the hospital. No formal exposure was stated, except for HF phenotype (ejection fraction category) and primary etiology (CAD-related *versus* nonCAD-related HF) for the fundamental survival analysis.

Statistical analyses we performed using STATISTICA 8 (StatSoft Inc, Tulsa, OK, USA) and STATA 8 (STATA Corp LP, College Station, TX, USA). Conventional descriptive methods were applied, i.e., the mean and standard deviation for continuous variables or frequency for categorical ones. Cox proportional hazard model was performed to identify the relative role of potential covariates on defined outcomes. Censored data were used for the final analysis. Power calculations revealed that our population of patients was sufficiently large to estimate the expected outcome incidence with a 5% relative precision level. Statistical significance was considered present at the p-value of 0.05.

Table 1. Baseline characteristics of study sample [mean (standard deviation) or percentual factor proportion].

n	097
Age [years]	70.7 (10.3)
Age >65 years [%]	75.2
Gender [% of males]	60.2
Length of hospitalization [days]	9.51 (8.0)
Hospitalization ≥10 days [%]	41.3
Coronary angiography [%]	55.3
Coronary revascularization [%]	27.8
History of smoking* [%]	21.6
Hypertension [%]	89.2
LDL-cholesterol [mmol/L]	2.28 (0.97)
LDL ≥1.8 mmol/L [%]	62.9
Fasting glycemia [mmol/L]	7.32 (2.54)
Diabetes mellitus†[%]	67.8
Estimated glomerular filtration‡ [mL/min]	48.0 (22.5)
Estimated glomerular filtration < 60 mL/min [%]	71.4
Peak brain natriuretic peptide ≥ 10times ULN $ [%]	56.3
Atrial fibrillation or flutter [%]	48.8
Known history of malignancy	10.4
Implanted cardioverter-defibrilator	14.3
Ejection fraction [%]	41.8 (14.9)
Ejection fraction categories [%]:	
HFrEF (EF ≤40%)	50.2
HFmrEF (EF 41-50%)	17.3
HFpEF (EF >50%)	29.0
Undertermined	3.5
Presumed primary etiology of HF[%]:	
Coronary artery disease	58.1
Hypertension	9.4
Dilated cardiomyopathy	8.5
Valvular heart disease	6.6
Tachycardia-induced KMP	8.0
Post-inflammatory KMP	0.5
Other/ undetermined	8.9
Pharmacotherapy:	
Antiplatelets	42.6
Oral anticoagulants	39.5
Furosemide	86.7
Betablockers (all)	77.5
Betablockers (evidence-based only§)	61.1
Renin-angiotensin system blockers	79.0
Mineralocorticoid receptor antagonists	45.3
Any other antihypertensive	27.9
Digoxin	12.6
Ivabradin	3.3
Statins	47.0
Antidiabetics	33.6

LDL, low-density lipoprotein; ULN, upper limit of normal; *past or current smoking; †highest fasting glucose ≥7 or non-fasting ≥11.1 mmol/L, history of diabetes and/or treatment with antidiabetics; ‡by CKD-EPI standard (highest creatinine value during hospitalization was used); $BNP ≥1000 ng/L or NT-proBNP ≥3000 ng/L; § bisoprolol, carvedilol, metoprolol-succinate or nebivolol

RESULTS

Baseline cross-sectional characteristics

The initial sample consisted of 4526 patients (with mean age 71.2 (±10.2) years, 59.5% were males) hospitalized for acute decompensation of HF between 2010 and 2020. From this initial cohort, 429 patients (9.5%) died during hospitalization.

The remaining 4097 patients were discharged from qualifying hospitalization and analyzed in this study. The baseline characteristics of the study sample are listed in Table 1. We identified 58.1 patients as CAD-related HF, while 41.9% were nonCAD-related (see Methods for definition of both subgroups).

Recommended pharmacotherapy

We listed the proportion of pharmacotherapy of particular interest (i.e., those with any prominent role in the treatment of HF or CAD, and as was recommended in the discharge summary) in Table 2. Patients with CAD-related HF had significantly more often recommended antiplatelets/anticoagulants, RAS blockers, and statins. They also had a significantly more frequently implanted cardioverter-defibrillator (ICD). Concerning EF categories, BB and MRAs were more often recommended in HFrEF than in HFmrEF and HFpEF, irrespective of HF etiology (CAD or nonCAD), and as expected, the same is true for ICD. Antiplatelets/ anticoagulants and statins were more frequently recommended in HFrEF in the CAD subgroup only, while RAS blockers in nonCAD-related HF patients.

We also analyzed the trends in these main therapeutic measures over time (across a year of hospitalization) (Fig. 1, top panel). A significant increasing trend over time was observed in MRAs prescription and ICDs, while the decreasing trend we observed in RAS blockers (*P* values adjusted for age and gender only). After more complex adjustment (age, gender, HF etiology and EF category), we observed following significant trend: in prescription of BB [Odds ratio for any year of hospitalization was 1.04 (95%CIs: 1.02–1.06), *P*<0.0001], MRAs [1.03 (95%CIs: 1.02–1.05), *P*=0.002], statins [1.09 (95%CIs: 1.06–1.11), *P*<0.0001] as well as ICDs [1.03 (95%CIs: 1.04–1.11), *P*<0.0001]. In contrast, the likelihood of having a prescribed RAS blocker significantly decreased over time [0.93 (95%CIs: 0.90-0.95), *P*<0.0001] (not in Table).

Mortality analysis

In total, 2206 patients died by 31.12.2020; median follow-up was 987 days (IQR: 366-1868). Standardized 30-days mortality was 3.2%, 1-year mortality (in 3821 subjects, with at least 1-year follow-up) 20.4%, while mortality between day 31 and 365 (n=3711, initially stabilized patients only) 18.0%. In patients hospitalized between 2010 and 2015 (n=2344), we also calculated 5- years mortality, which was 55.4%, or 54.1%, if those deceased during the first 30 days after admission were excluded.

Fig. 1 (bottom panel) shows the standardized mortality according to the year of hospitalization. We observed statistically significant differences in 30-days mortality

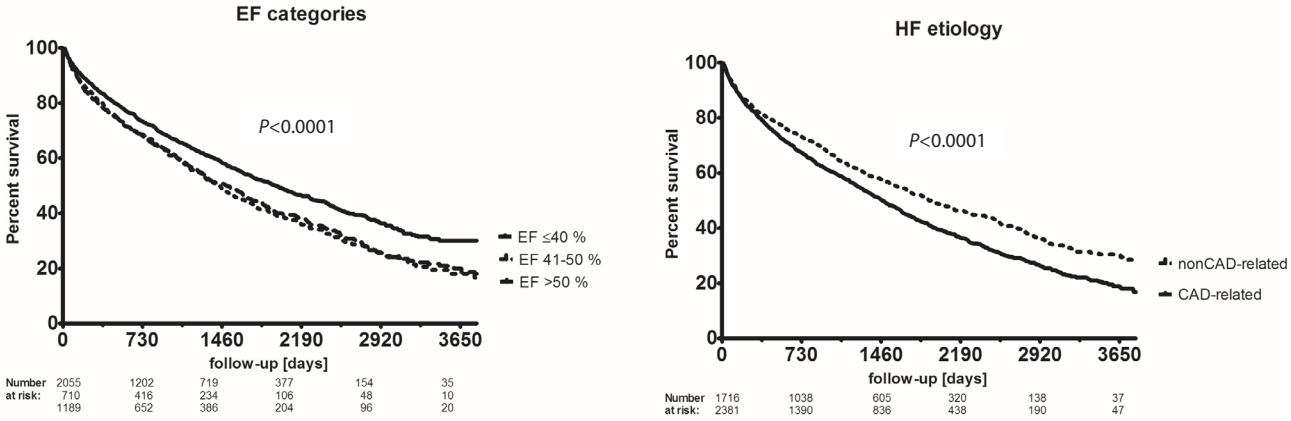

Fig. 1. Kaplan-Meier survival curves for ejection fraction and primary HF etiology categories. *P* value by Mantel-Cox log-rang test.

between years of hospitalization, but any apparent trend can not be discriminated. 5-year mortality does not significantly change across a year of hospitalization (in patients hospitalized between 2010 and 2015 only). No apparent differences in 1-year mortality between 2010–2016 can be discriminated (Fig. 1), but there was a moderate decrease in the last three years of observation (2017–2019). Using 2010–16 as the reference, HRR for 1-year mortality risk in 2017–2019 was 0.84 (95%CIs: 0.71–0.99), *P*=0.050, adjusted for age, gender, CAD-related etiology, EF category, and history of malignancy (not in Table). Moreover, a significant trend to decreased mortality overtime was also confirmed in the fully adjusted model (Table 3); any increase of year of hospitalization by one was associated with about 5% lower risk of 1- years mortality risk.

Kaplan-Meier survival curves comparing three main HF phenotypes (EF categories) are in Fig. 1 (left panel). Using EF >50% subgroup as the reference (with the risk equal to 1), the 1-year hazard risk ratio was for EF 41–50% subgroup 0.92 (95%CIs: 0.75–1.13), *P*=0.423, while for EF ≤40% subgroup 0.83 (95%CIs: 0.70–0.99), *P*=0.037 (adjusted for age, gender, HF etiology and history of malignancy).

No significant difference we observed for survival regarding the primary etiology of HF (Fig. 1, right panel). In the adjusted model (age, gender, EF category, and history of malignancy), 1-year mortality HRR for CAD-related etiology was 1.13 (95%CIs: 0.98–1.31), *P*=0.085.

In Table 3, we analyzed 1-year mortality predictors in the context of all available potential covariates (model A). Positive predictive power (increased mortality risk) we identified for age over 65, history of malignancy, and markedly increased BNP during hospitalization. As a protective factor regarding 1-year mortality risk, we identified LDL ≥1.8 mmol/L, treatment with BB, RAS blockers, statins, and ICD. Consequently, we repeated the same regression but included only subjects who survived at least 30 days after admission into the hospital (i.e., the most severely ill patients were excluded)- model B. The results were more-than-less similar, but additionally, significantly increased mortality risk we observed for hospitalization ≥10 days. Model C consisted only of patients with at least 5-year follow-up (i.e., hospitalized between 2010 and 2015) and those who survived at least 30 days after admission. The significantly increased risk was associated with age over 65, hospitalization ≥10 days, CAD-related HF etiology, markedly increased BNP during hospitalization and treatment with antiplatelets or anticoagulants. On the other hand, from evaluated therapeutic measures, the protective potential was observed only for statins and ICD. We also repeated all three models but using only evidence-based BB instead of all BB as covariates (and if subjects treated with non-evidence-based BB were excluded), the results were nearly similar. Finally, we excluded from the model all patients with a history of malignancy. Again, the results were confirmatory.

DISCUSSION

The key message of our analysis is that despite all the progress that has been made in cardiovascular medicine in the last two decades, the mortality of heart failure patients remains enormous. Though "only" 3.2% of discharged patients died during the first 30 days after hospital admission, to determine the early mortality impact from heart failure correctly, we should also include patients who died already during hospitalization. Taking in-hospital fatality also into account, 11% of patients under the age of 86 years died in our initial cohort within 30 days after admission. We also similarly observed a high mortality risk for the initially stabilized patient. Despite surviving the first 30 days, another ≈17% (from the initial pool) died during the 1st year, while ≈54% during five years.

The mortality risk of patients hospitalized for the heart "stands out," especially when compared to, for example, the prognosis of patients after myocardial infarction. In another sample of patients hospitalized for myocardial infarction in the same hospital and at about the same time (2006-2018), patients under the age of 86 had ≈4% early mortality within 30 days of admission (including in-hospital death), ≈6% mortality between day 31 and year 1, while 34% between day 31 and year 5 (ref.[4]). The mortality observed in our analysis (28% during 1st year, including

Table 2. Prescription [%] of guidelines-determined therapy by heart failure phenotype (ejection fraction categories) and according to primary presumed etiology.

	CAD (n=2381)	**nonCAD** (n=1716)	***P*$^{\$}$**
All Subjects (n=4097):			
Antiplatelets or anticoagulants	87.2	64.3	<0.001
Furosemide	86.8	86.7	0.915
Beta-blockers (evidence-based only*)	59.3	56.9	0.672
Renin-angiotensin system blockers†	80.5	76.9	0.005
Mineralocorticoids receptor antagonists‡	45.2	45.5	0.838
Statins	57.2	32.8	<0.001
Implanted cardioverter-defibrilator	17.4	10.0	<0.001
HFrEF (n=2055):			
Antiplatelets or anticoagulants	89.9	63.7	<0.001
Furosemide	87.8	85.9	0.955
Beta-blockers (evidence-based only*)	68.5	70.4	0.294
Renin-angiotensin system blockers†	81.0	80.3	0.711
Mineralocorticoids receptor antagonists‡	54.3	57.3	0.611
Statins	62.9	34.3	<0.001
Implanted cardioverter-defibrilator	30.3	21.9	<0.001
HFmrEF (n=710):			
Antiplatelets or anticoagulants	86.2	69.6	<0.001
Furosemide	84.5	85.9	0.017
Beta-blockers (evidence-based only*)	50.1	49.8	0.638
Renin angiotensin system blockers†	80.6	76.7	0.364
Mineralocorticoids receptor antagonists‡	36.7	35.3	0.913
Statins	51.1	35.3	<0.001
Implanted cardioverter-defibrilator	2.1	3.5	0.113
HFpEF (n=1188):			
Antiplatelets or anticoagulants	83.3	64.1	<0.001
Furosemide	86.1	87.7	0.629
Beta-blockers (evidence-based only*)	47.4	45.8	0.939
Renin angiotensin system blockers†	80.4	80.4	0.214
Mineralocorticoids receptor antagonists‡	33.5	36.1	0.854
Statins	51.1	31.9	<0.001
Implanted cardioverter-defibrilator	0.9	1.1	0.052
***P* for trend** across heart failure phenotype:			
Antiplatelets or anticoagulants	<0.001	0.391	
Furosemide	0.241	0.596	
Beta-blockers (evidence-based only*)	<0.001	<0.001	
Renin angiotensin system blockers†	0.288	<0.001	
Mineralocorticoids receptor antagonists‡	<0.001	<0.001	
Statins	<0.001	0.10	
Implanted cardioverter-defibrilator	<0.001	<0.001	

CAD, coronary artery disease; HFrEF, heart failure with reduced ejection fraction (i.e. ≤40%); HFmrEF, heart failure with mid-range ejection fraction (i.e. 41-50%); HFpEF, heart failure with preserved ejection fraction (i.e. >50%); subject with undetermined ejection fraction (n=144) excluded from this analysis; *bisoprolol, carvedilol, metoprolol-succinate or nebivolol; †angiotensin-converting enzyme inhibitors or sartans (incl. ARNI´s); ‡spironolactone or eplerenone; $CAD *versus* nonCAD

in-hospital deaths) is also relatively high compared with other countries. For example, data from 3 German health insurance providers (≈109 000 analyzed subjects) showed that the 1-year mortality was in patients hospitalized for HF 23% in 2006 (ref.[5]) In another older studies (total ≈117 000 patients from the UK and Canada,time-span of hospitalizations 1986–2001) ranged 1- year mortality in 21–44% (ref.[6-8]). A more recent study by Lin and colleagues (≈51 000 subjects from the US, time-span of hospitalizations 2007–2011) found that 30 days and 1-year mortality in heart failure patients were 7.4% a 27.3%, respectively[9]. Therefore, patients hospitalized for heart failure represents a crucial part of the global burden of cardiovascular disease in the Czech Republic and should be given special attention in health policy-making.

Another important message is that the mortality of hospitalized heart failure patients does not yet change convincingly. This observation is seemingly in conflict with the unequivocal and continuous trend of declining cardiovascular mortality in the Czech Republic after 1990 (ref.[10]). On the other hand, this favorable trend is primarily driven by a decrease in the incidence of myocardial infarction and its fatality in the acute phase[11]. As can be expected, improved survival acute phase of CAD leads

Table 3. Predictors of all-cause mortality (Cox proportional hazard model).

	1-year mortality (all subjects †) model A		1-year mortality (excl. early deceased) ‡ model B		5-year mortality (excl. early deceased) $ model C	
	HRR (95% CI's)	*P*	HRR (95% CI's)	*P*	HRR (95% CI's)	*P*
Age >65 years	1.82 (1.32–2.51)	<0.0001	2.01 (1.41–2.87)	<0.0001	1.86 (1.46–2.36)	<0.0001
Male gender [% of males]	1.18 (0.94–1.47)	0.151	1.18 (0.93–1.49)	0.170	1.19 (0.99–1.41)	0.051
Year of hospitalization*	0.95 (0.92–0.99)	0.012	0.95 (0.91–0.99)	0.038	1.01 (0.96–1.06)	0.794
Hospitalization ≥10 days	1.20 (0.97–1.49)	0.090	1.29 (1.03–1.62)	0.028	1.29 (1.10–1.52)	0.002
Coronary artery disease as primary etiology	1.12 (0.86–1.44)	0.399	1.12 (0.85–1.46)	0.426	1.22 (1.01–1.47)	0.040
Coronary revascularization	1.00 (0.76–1.32)	0.987	0.95 (0.71–1.27)	0.719	0.91 (0.74–1.13)	0.394
History of malignancy	1.48 (1.10–1.99)	0.010	1.40 (1.02–1.93)	0.038	1.25 (0.93–1.67)	0.147
Atrial fibrillation or flutter	0.99 (0.79–1.23)	0.927	0.96 (0.76–1.21)	0.740	0.90 (0.76–1.07)	0.244
Ejection fraction ≤40%	1.06 (0.84–1.33)	0.635	1.06 (0.83–1.35)	0.639	1.04 (0.87–1.24)	0.654
Current or ex-smoking	0.83 (0.62–1.13)	0.256	0.85 (0.62–1.17)	0.330	1.13 (0.90–1.42)	0.311
Hypertension	1.00 (0.67–1.50)	0.985	1.03 (0.67–1.60)	0.883	1.30 (0.91–1.84)	0.145
LDL ≥1.8 mmol/L	0.74 (0.60–0.92)	0.007	0.74 (0.59–0.93)	0.009	0.90 (0.76–1.08)	0.267
Diabetes mellitus	1.09 (0.87–1.38)	0.453	1.08 (0.84–1.38)	0.566	1.20 (1.00–1.44)	0.054
Estimated glomerular filtration <60 mL/min	1.15 (0.87–1.51)	0.317	1.14 (0.85–1.53)	0.375	1.09 (0.88–1.36)	0.424
Brain natriuretic peptide ≥10times ULN	1.74 (1.38–2.21)	<0.0001	1.91 (1.49–2.46)	<0.0001	1.35 (1.15–1.60)	<0.0001
Antiplatelets or anticoagulants	0.84 (0.65–1.10)	0.207	0.96 (0.72–1.28)	0.759	1.39 (1.11–1.75)	0.005
Furosemide	0.99 (0.68–1.45)	0.975	0.94 (0.63–1.39)	0.746	1.32 (0.97–1.80)	0.078
Beta-blockers	0.78 (0.61–0.99)	0.041	0.75 (0.58–0.96)	0.022	0.91 (0.75–1.10)	0.317
Renin-angiotensin system blockers	0.70 (0.55–0.90)	0.005	0.75 (0.58–0.98)	0.032	0.82 (0.66–1.02)	0.073
Mineralocorticoids receptor antagonists	0.97 (0.78–1.20)	0.764	1.00 (0.80–1.25)	0.995	0.96 (0.81–1.13)	0.601
Statins	0.74 (0.59–0.93)	0.010	0.74 (0.58–0.94)	0.015	0.83 (0.70–0.99)	0.037
Implanted cardioverter-defibrilator	0.52 (0.31–0.87)	0.014	0.44 (0.24–0.81)	0.008	0.49 (0.31–0.75)	0.001

HRR, hazard risk ratio; CI's, confidence intervals; ULN, the upper limit of normal; *2010, 2011... 2019; for definitions of all other variables see Methods or Table 1; †all patients hospitalized between 2010 and 2019 (n=3821), ‡hospitalized between 2010 and 2019 and only the survivors of at least 30 days after hospital admission (n=3711), $hospitalized between 2010 and 2015 and only the survivors of at least 30 days after hospital admission (n=2277)

to increased prevalence not only of the chronic form of this disease but also more complications (such as HF). Although we observed a significant decrease in 1-year mortality in the last three evaluable seasons (2017–2019), resulting in a 16% decrease of relative risk of all-cause death (using the period 2010–2016 as a reference). However, this period with a relative reduction of mortality risk is still too short of making any conclusion, and we must wait to see if this favorable trend will be confirmed in the years to come.

In the context of mortality, we also analyzed the role of potential covariates of individual risk. As expected, age was the main covariate of fatal outcomes (regardless of the time horizon in which the death was to occur). Marginally higher mortality risk (with borderline significance only) we observed for the male gender, but only if 5-years mortality was calculated (and in a fully adjusted model only, Table 3). The primary etiology (i.e., CAD or nonCAD related) does not significantly affect consequent mortality risk. The exception was 5-year mortality again (after exclusion of early deceased patients), showing about 20% higher risk associated with CAD-related etiology of HF. Surprisingly, HFrEF patients showed a slightly better prognosis than HFpEF or HFmrEF subjects, having significantly lower relative risk (by 17%) of all-cause death during 1st year. This unexpected phenomenon probably reflects that HFrEF patients had more complex therapy than the HFpEF patients (see Table 2). The statistical significance of this difference we observed in the partially adjusted model only, while wholly disappeared if data about therapy and other confounding factors were added into the regression model. HFrEF patients are also slightly younger (68.4 *versus* 73.3 years, respectively), while are more often males (71.0 *versus* 44.0%, respectively) than those with HFpEF. In contrast to another paper[12], we also observed that the prevalence of HFrEF among all hospitalized patients slightly increased during 2010–2020 [taking EF <40% as the dependent variable, odds ratio for the year of hospitalization was 1.04 (1.02–1.06), *P*<0.0001; adjusted for age, gender a CAD-related HF)] (not in Results).

Comorbidities and the identifiable circumstances of the hospitalization did not significantly affect the mortality risk, but they are some exceptions. After excluding early deceased patients (i.e., perhaps those most severely ill), prolonged hospitalization (≥10 days) signals about a 30% higher mortality risk. The reason is apparent, as these patients are likely to have more severe heart failure

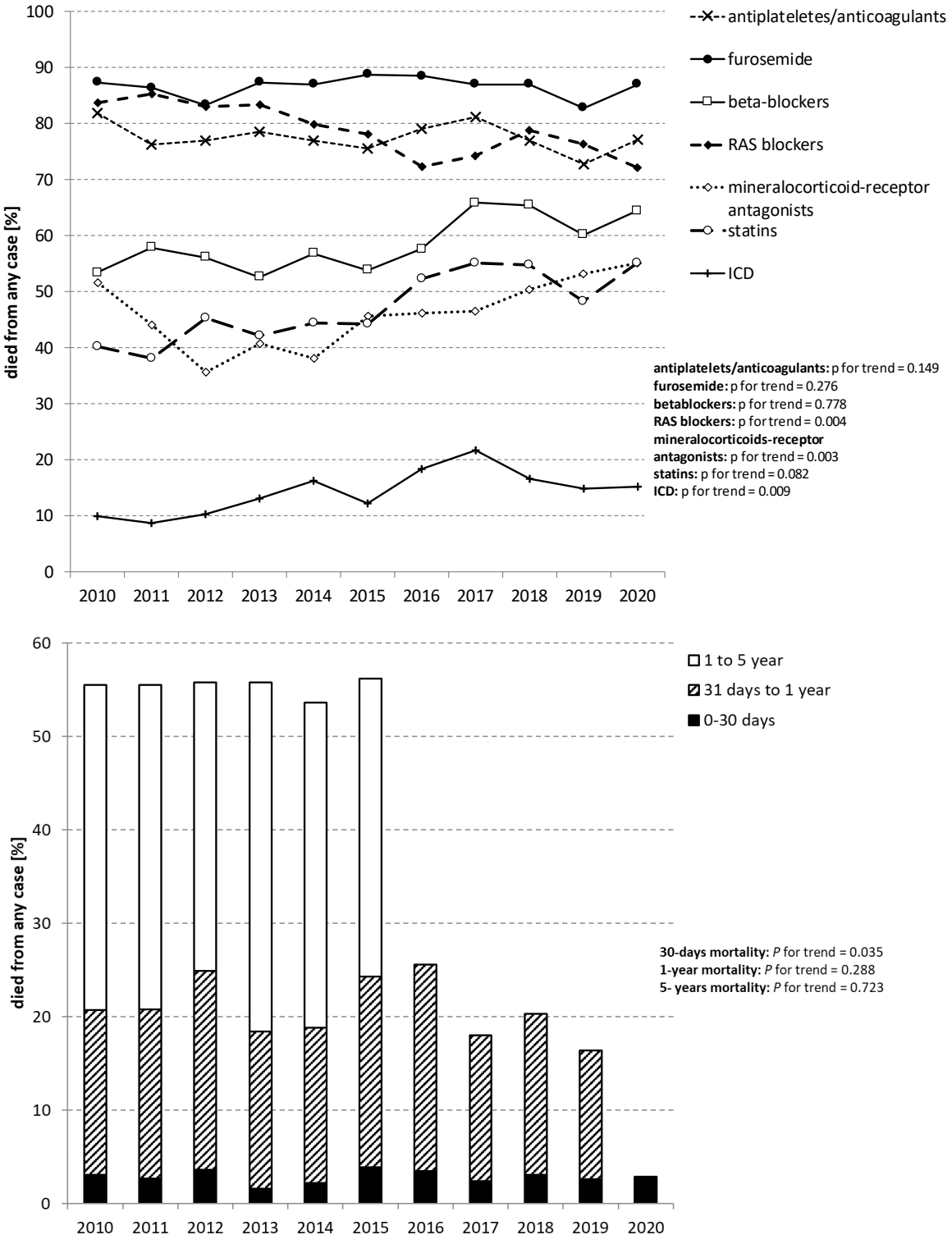

Fig. 2. Changes in the prescription of essential heart failure therapy and standardized mortality during the years 2010–2020. *P* value by Kruskal-Wallis ANOVA.

staging. History of malignancy (independently of its grading/staging) significantly increased risk of death during 1st year after admission, but not 5-years mortality risk. We can speculate that phenomenon reflects the fact that predominantly advanced stanging of malignancy hardly influence the prognosis of HF patients (and cardiac decompensation can be one of the complications of malignancy or its treatment). In contrast, in patients with long-term remission, less aggressive forms of malignant diseases, or favorable grading/staging, the fact of heart failure requiring hospitalization is probably a more fundamental negative prognostic factor than the history of malignancy itself. The overall results of our analysis were also unaffected if patients with a history of malignancy were utterly excluded. Another prognostically important factor represents markedly increased BNP during hospi-

talization (peak concentration ≥1000 ng/L or 3000 ng/L, for BNP or NT-proBNP, respectively). This observation is entirely in line with the well-established role of natriuretic peptides in HF. Prognostic significance of increased natriuretic peptides was demonstrated in HF patients[13], especially for values obtained during hospitalization[14].

One of the primary goals of our analysis was to assess the extent to which the prescription of essential pharmacotherapy and other measures met current standards and how the situation has changed over the years. Prescription of RAS blockers is entirely satisfactory (≈81%), significantly higher in CAD than in nonCAD- related HF, and nearly similar across all three ejection fraction categories. For unknown reasons, the prescription of RAS decreased over time from ≈82% in 2010-2015 to ≈75% in 2016-2020. In concert with established evidence[15,16], we also observed a significant mortality benefit associated with the prescription of RAS blockers (despite only for 1-year mortality risk).

Prescription of evidence-based BB (ref.[17-20]) (bisoprolol, carvedilol, metoprolol-succinate, and nebivolol) ranged from ≈53 to 66% and slightly (non-significantly) increased over time between 2010 and 2020. There is also a clear gap in the prescription of BB between HFrEF and HFpEF or HFmrEF, while no difference between CAD and nonCAD-related HF. Another 16.1% of patients were prescribed BB lacking evidence in HF and should therefore not be used in this indication[2] (or instead, should be replaced by evidence-based BB). Indeed, prescription of BB was in our sample associated with significantly decreased the risk of 1-year mortality, nearly in the nearly same extent if all BB or only evidence-based ones were taken into account. Due to the retrospective design of our study, this is not proof that the choice of BB type does not play a role in HF.

Prescription of mineralocorticoid-receptor antagonists (MRAs, i.e. spironolactone or eplerenone) significantly raised over time between 2010 and 2020, when it reached about 55%. As expected and in concert with available evidence[21,22], MRAs are more often prescribed in HFrEF than HFpEF or HFmrEF patients. It may also be speculated that more extensive prescriptions raise concerns about the side effect (hyperkalemia). However, newer representatives of this pharmacological class, with a much safer profile (namely finerenone), could overcome this problem in the future[23]. A study is also underway (FINEARTS-HF) to provide us with data on the effectiveness of this new preparation in HFpEF.

A specific question represents lipid levels and the prescription of statins. We observed that low LDL levels were paradoxically accompanied by increased mortality. This phenomenon (sometimes called "reverse epidemiology") was also observed in several other cohorts of chronic HF heart failure patients[24-26], in both CAD and nonCAD-related HF, as well as in other advanced chronic diseases. It is caused probably primarily by the observational (non-interventional) design of our analysis, and low cholesterol probably only reflects progressive severity of HF, with consequent higher mortality risk. There are several hypotheses regarding the exact mechanism of this phenomenon, including malnutrition and increased inflammatory activity[24,27]. Statin treatment was in our study associated with improved survival, and to the nearly same extent in CAD or nonCAD-related HF. It is no doubt about an indication of statin in CAD, therefore also in CAD-related HF should be this drugs a part of treatment (and in the present analysis, it was only in ≈57% of patients). A meta-analysis of 6 intervention trials in patients with CAD (recently after myocardial infarction) showed that intensive statin therapy reduced the risk of hospitalization for HF (ref.[28]). The mortality risk reduction associated with this drug class is also proven convincingly in another large meta-analysis[29]. However, the evidence does not support the general use of statin in HF (i.e., also in nonCAD-related) since two interventional trials (CORONA and GISSI-HF) did not show any convincing benefit of this treatment[30,31]. Based on a meta-analysis of 13 interventional studies[32], statin may also slightly lessen the chance o subsequent coronary event (still, only a minority of HF patients die from acute coronary syndrome). On the other hand, there is probably no reason to stop already prescribed statin when HF develops unless statin-related complications arise.

The last important part of HF management that needs to be mentioned is ICD. This implantable device represents the only available treatment proven to prevent arrhythmic sudden cardiac death. The guidelines recommend the ICDs in HF patients with an EF ≤35% despite at least three months of optimal medical treatment[2]. Interventional studies demonstrated the benefit in this "primary prevention" context; the mortality risk reduction was ≈30% over five years[33,34]. Despite that, ICDs remained in several countries underutilized and highly regulated by health insurance providers. In our sample, ICDs were implanted in ≈27% of HFrEF patients and with an increasing trend (23.5% in 2010–2015, while 31.8% in 2016–2020). We also observed a ≈50% mortality risk reduction associated with ICDs.

Besides above mentioned main drug classes, also new treatment possibilities raised in the last years. However, they were prescribed in our sample minimally (entirely unsurprising, because they are either introduced into practice relatively recently or are highly regulated by the health insurance providers). For the purpose of our analysis, we included ARNIs (angiotensin receptor –neprilysin inhibitors) in the RAS blockers group since its prescription was marginal (only 37 patients, i.e., 0.9%). Similarly minimal was the prescription of ivabradine (3.3%) and sodium-glucose co-transporter 2 inhibitors (only 28 subjects, i.e., 0.7%)- we have omitted them entirely from the analysis. The newest drugs in HF, already mentioned in the Guidelines[2] (such as vericiguat), have not yet been implemented.

Study limitations

First, our study sample consisted without any doubt of very severely-ill subjects because the mere fact that hospitalization for decompensation has taken place shows that chronic HF in these patients has reached a relatively advanced stage. Thus, our observations (especially in terms of mortality risk) are probably not (perhaps) fully

generalizable, for example, in long-term stable HF patients requiring only outpatient care.

Second, we used only the first hospitalization during the observation period 2010–2020, and we have a 10-year look-back (2001–2009) available for our patients regarding the previous hospitalization for HF. Thus, most hospitalization for HF probably represents the first event of cardiac decompensation requiring hospitalization. On the other hand, we have no data about HF hospitalization before 2001 and individual cases of worsening heart failure, which are addressed only in the outpatient setting. Moreover, we don't know precisely the duration of heart failure, which is undoubtedly an essential prognostic indicator and whose influence we could not consider in our analysis.

Finally, due to newly adopted GDPR rules, it's impossible currently to obtain data from the national register of hospitalizations. Therefore we could not analyze the incidence of rehospitalization for HF.

CONCLUSIONS

The prognosis of patients with heart failure, whose staging (progression) already forces hospitalization, is highly unfavorable; almost a third die within one year and more than half within 5 years. Moreover, due to the improved survival of the acute phase of ACS, the burden of the health care system due to heart failure can be expected to increase in the future. Management of the patients with advanced heart failure is far from being optimal, and, for example, more excellent centralization of the care of these patients in specialist outpatient clinics would be helpful. New drug groups and other therapeutic measures (such as ICDs) also have great potential for improving the prognosis of patients with heart failure.

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