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Assessment of the complex treatment of heart failure with reduced ejection fraction and its impact on long-term prognosis

Summary of PhD Thesis

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1 PUBLICATIONS

1.1 Related to the Thesis

1. **Bánfi-Bacsárdi F,** Muk B, Pilecky D, Duray GZ, Kiss RG, Nyolczas N. The Optimization of Guideline-Directed Medical Therapy during Hospitalization among Patients with Heart Failure with Reduced Ejection Fraction in Daily Clinical Practice. Cardiology. 2023;148(1):27-37. doi: 10.1159/000528505.
IF: 1.9

2. **Bánfi-Bacsárdi F,** Pilecky D, Vámos M, Majoros Z, Török GM, Borsányi TD, Dékány M, Solymossi B, Andréka P, Duray GZ, Kiss RG, Nyolczas N, Muk B. The effect of kidney function on guideline-directed medical therapy implementation and prognosis in heart failure with reduced ejection fraction. Clin Cardiol. 2024;47(2):e24244. doi: 10.1002/clc.24244.
IF: 2.7

3. Muk B, **Bánfi-Bacsárdi F,** Vámos M, Pilecky D, Majoros Z, Török GM, Vágány D, Polgár B, Solymossi B, Borsányi TD, Andréka P, Duray GZ, Kiss RG, Dékány M, Nyolczas N. The Impact of Specialised Heart Failure Outpatient Care on the Long-Term Application of Guideline-Directed Medical Therapy and on

Prognosis in Heart Failure with Reduced Ejection Fraction. Diagnostics (Basel). 2024;14(2):131. doi: 10.3390/diagnostics14020131.
IF: 3.6

1.2 Not directly related to the Thesis

4. **Bánfi-Bacsárdi F,** Vámos M, Majoros Z, Török G, Pilecky D, Duray GZ, Kiss RG, Nyolczas N, Muk B. [The effect of kidney function on the optimization of medical therapy and on mortality in heart failure with reduced ejection fraction]. Orv Hetil. 2023;164(35):1387-1396. doi: 10.1556/650.2023.32836.
IF: 0.8

5. Solymossi B, Muk B, Sepp R, Habon T, Borbély A, Heltai K, Majoros Z, Járai Z, Vágány D, Szatmári Á, Sziliczei E, **Bánfi-Bacsárdi F,** Nyolczas N. Incidence and predictors of heart failure with improved ejection fraction category in a HFrEF patient population. ESC Heart Fail. 2024;11(2):783-794. doi: 10.1002/ehf2.14619.
IF: 3.2

6. Muk B, Pilecky D, **Bánfi-Bacsárdi F,** Füzesi T, Gergely GT, Komáromi A, Papp E, Szőnyi MD, Forrai Z, Kazay Á, Solymossi B, Vámos M, Andréka P, Piróth Z, Nyolczas N. [The changes in the pharmacotherapy of heart failure with reduced ejection fraction and its effect on prognosis: experience in the Hungarian clinical practice]. Orv Hetil. 2024;165(18):698-710. doi: 10.1556/650.2024.33045.
IF: 0.8

7. Gergely TG, **Bánfi-Bacsárdi F**, Komáromi A, Pilecky D, Boldizsár EM, Flegler D, Kazay Á, Füzesi T, Forrai Zs, Vértes V, Sayour VN, Andréka P, Piróth Zs, Nyolczas N, Muk B. [Rapid up-titration of guide-directed medical therapy after a heart failure hospitalisation]. Orv Hetil. 2024;165(31):1197–1205. doi: 10.1556/650.2024.33081.
IF: 0.8

8. **Bánfi-Bacsárdi F,** Boldizsár EM, Gergely TG, Forrai Zs, Kazay Á, Füzesi T, Hanuska LF, Schäffer PP, Pilecky D, Vámos M, Gavallér Z, Keresztes K, Dékány M, Andréka P, Piróth Zs, Nyolczas N, Muk B. [The role of complex patient education program in heart failure care]. Orv Hetil. 2024;165(37):1461-1471. doi: 10.1556/650.2024.33121.
IF: 0.8

9. **Bánfi-Bacsárdi F**, Ormos F, Muk B. [The importance of chronic kidney disease in the management of patients with heart failure]. Cardiol Hung. 2024;54(3):206-211. doi: 10.26430/CHUNGARICA.2024.54.3.206

2 INTRODUCTION

Heart failure (HF) is one of the leading cardiovascular diseases, affecting more than 64 million people worldwide. Although treatment options for HF have expanded within the past decades, the related prognosis is still comparable to that of the most common cancers.

Regarding the complex care of HF with reduced ejection fraction (HFrEF), pharmacotherapy still represents the cornerstone of treatment. First-line drug treatment has changed significantly within the last decade. In light of the PARADIGM-HF trial, the 2016 ESC HF Guidelines (GLs) recommended a change of the previously applied renin-angiotensin system inhibitor (RASi) to an angiotensin receptor-neprilysin inhibitor (ARNI) in the case of persisting symptoms. The 2021 ESC HF GLs led to an additional paradigm shift in the medical therapy of HFrEF. The conventional first-line pillars of the medical therapy, being RASi-s (angiotensin-converting enzyme inhibitor [ACEi]/ARNI/angiotensin receptor blocker [ARB] in the case of ACEi and ARNI intolerance), β blockers (βB) and mineralocorticoid receptor antagonists (MRA) were supplemented with the sodium-glucose co-transporter 2 inhibitor (SGLT2i) dapagliflozin/empagliflozin based on the results of the DAPA-HF and EMPEROR-Reduced trials. These drugs are recommended for all

patients with HFrEF in the absence of a contraindication/intolerance (Class of recommendation: I, Level of evidence [LoE]: A for ACEi, βB, MRA and SGLT2i medications; B for ARNI; C for ARB). Besides this expansion of the morbidity and mortality-reducing armamentarium of the pharmaceutical therapeutic options in HFrEF, the hierarchic therapy implementation strategy suggested by the 2016 and previous ESC HF GLs has been replaced with a more comprehensive therapy optimisation philosophy, aspiring for the early introduction of the four first-line pillars of HFrEF (quadruple therapy [QT]: RASi+βB+MRA+SGLT2i) and the up-titration of guideline-directed medical therapy (GDMT). Time-to-GDMT has a striking effect on prognosis. Thus, clinicians should take every opportunity to optimise medical therapy, including hospitalisation, as in-hospital-adjusted GDMT strongly impacts long-term pharmacotherapy and prognosis.

Despite the strong evidence and clear instructions about the initiation of GDMT suggested by the current HF GLs, the application rate of the prognosis-modifying drug regime often remains undesirably low in everyday clinical practice. The reasons for GDMT underuse and clinical inertia have come under the spotlight

Comorbidities are also of major relevance in the holistic management of HF, as they can interfere with the diagnosis and the complex management of the underlying HF at several points. These comorbidities may also adversely affect the introduction and dose

titration of GDMT in HFrEF. Kidney dysfunction/chronic kidney disease (CKD) is one of the most prominent, yet one of the most underdiagnosed comorbidities in HF.

Paradoxically, patients who have advanced kidney dysfunction in addition to HF, and therefore have an increased risk of mortality and morbidity, are less likely to be treated with prognosis-modifying GDMT in the daily practice.

The strategic importance of HF Outpatient Care (HFOC) cannot be overemphasised in the complex, holistic management of HFrEF. Despite the current international GLs, HFOC is not broadly established and reimbursed worldwide, including Hungary. After the publication of data on the impact of HFOC on the prognosis of patients with HFrEF, a paradigm-shift has taken place in the pharmacotherapy of HFrEF, so it should be emphasized that HFOC requires further studies to evaluate its impact on the use of modern GDMT, long-term drug adherence and prognosis.

3 AIMS

3.1 In-hospital therapy-optimisation of patients hospitalised for HFrEF

In a consecutive, real-world cohort of HFrEF patients hospitalised for HF, we aimed

- to evaluate the application rate of GDMT at hospital admission and discharge,
- to assess the independent predictors of the discharge application of conventional triple therapy (TT: RASi+βB+MRA),
- to assess the potential applicability of novel HFrEF medications (ARNI, SGLT2i, vericiguat).

3.2 The role of kidney dysfunction in the therapy-optimisation and prognosis of HFrEF patients

In a consecutive, real-world cohort of HFrEF patients hospitalised for HF, we aimed

- to assess the application ratio of complex neurohormonal antagonist therapy (RASi: ACEi/ARB/ARNI, βB, MRA) according to the severity of kidney dysfunction at hospital discharge and at 1 year of follow-up (FUP),

- to evaluate the proportion of patients receiving target doses of neurohormonal antagonist therapy according to the severity of kidney dysfunction at hospital discharge and at 1 year,
- to evaluate therapy adherence during 1-year FUP period,
- to examine 1-year prognosis (all-cause mortality, all-cause hospitalisation, cardiovascular rehospitalisation, and rehospitalisation for acute HF (AHF) across the whole spectrum of kidney dysfunction,
- to assess the independent predictors of the application of TT at discharge and of the 1-year all-cause mortality.

3.3 The impact of HFOC on the long-term application of GDMT and prognosis in HFrEF

In a consecutive, real-world cohort of HFrEF patients hospitalised for HF, we aimed

- to evaluate the impact of HFOC after the index hospitalisation on the application rate and achieved target doses of GDMT,
- to analyse the effect of HFOC on the composite endpoint of 1-year all-cause mortality and rehospitalisation,

- to analyse the effect of HFOC on the composite endpoint of 1-year all-cause mortality and rehospitalisation after propensity-score matching (PSM),
- to investigate the independent predictors of 1-year all-cause mortality and all-cause rehospitalisation in HFrEF patients after hospitalisation for HF.

4 STUDY DESIGN

4.1 In-hospital therapy-optimisation of patients hospitalised for HFrEF

The data of a consecutive, real-world HFrEF patient cohort hospitalised for HF between 01.01.2019 and 31.10.2021 at the HF Unit of the Medical Centre, Hungarian Defence Forces, were analysed retrospectively. The admission diagnosis of ongoing acute coronary syndrome and in-hospital mortality formed exclusion criteria. The first event was considered to avoid redundancy in the case of multiple HF hospitalisations during the data collection period. The study was approved by the Institutional Research Ethics Committee of the Hungarian Defence Forces Medical Centre (approval number KK00/144-1/2022) and was undertaken in conformity with the Helsinki Declaration.

The application rate of conventional neurohormonal antagonist therapy was assessed by comparing medication at hospital admission and discharge. Even though the results of SGLT2i landmark trials were only published during our research period and implemented in the 2021 ESC HF GLs (thus at the end of our data collection period), we also investigated the application rate of dapa- and empagliflozin. The predictive value of factors potentially influencing the discharge utilisation of TT was evaluated in the univariate- and multivariate logistic regression analysis. The theoretical application rate of novel HFrEF pharmacotherapies (ARNI, SGLT2i, vericiguat) was also analysed.

4.2 The role of kidney dysfunction in the therapy-optimisation and prognosis of HFrEF patients

A consecutive group of real-world patients with HFrEF hospitalised for HF between 01.01.2019 and 31.10.2021 at the HF Unit of the Department of Cardiology, Medical Centre, Hungarian Defence Forces, tertiary cardiology centre was analysed retrospectively. Intrahospital mortality was an exclusion criterion. In the case of multiple hospitalisations of individual patients during the data collection period, the first event was considered in the analysis to avoid redundancy. The FUP period was 1 year for all patients. The

study protocol was reviewed and approved by the Institutional Research Ethics Committee of the Hungarian Defence Forces Medical Centre (approval number: KK00/144-1/2022), and the investigation conforms with the principles outlined in the Declaration of Helsinki.

In concordance with the Kidney Disease: Improving Global Outcomes (KDIGO) classification, patients were classified into five groups based on the severity of the kidney dysfunction defined using hospital estimated glomerular filtration rate (eGFR) parameters measured at hospital discharge: eGFR ≥ 90 mL/min/1.73m^2, eGFR = 60-89 mL/min/1.73m^2, eGFR = 45-59 mL/min/1.73m^2, eGFR = 30-44 mL/min/1.73m^2, eGFR < 30 mL/min/1.73m^2. We evaluated the proportion of patients experiencing significant eGFR decrease occurring within index hospitalisation (defined as > 15% decline in eGFR value between admission and discharge). The application ratio of neurohormonal antagonist therapy, its target dose application ratio, and 1-year prognosis (all-cause mortality, all-cause hospitalisation, cardiovascular rehospitalisation, and rehospitalisation for AHF) were evaluated according to kidney dysfunction categories. Therapy adherence was assessed at 1 year of FUP. The independent predictors of the application of TT at hospital discharge and 1-year all-cause mortality were also considered.

4.3 The impact of HFOC on the long-term application of GDMT and prognosis in HFrEF

We undertook a retrospective observational study, evaluating a consecutive, non-selected group of real-world HFrEF patient cohort hospitalised for HF between 01.01.2019 and 31.10.2021 in the HF Unit of the Department of Cardiology, Medical Centre, Hungarian Defence Forces. In-hospital mortality formed an exclusion criterion. In case of repetitive hospitalisation in the examined period, the first hospitalisation was considered to avoid redundancy. Patients were followed up for 1 year. All patients were offered FUP at HFOC after hospital discharge; its acceptance was voluntary. Our retrospective observational study protocol was reviewed and approved by the Institutional Research Ethics Committee of the Medical Centre, Hungarian Defence Forces (approval number: KK00/144-1/2022.), and the present study adheres to the ethical principles of the Declaration of Helsinki.

The application ratio- and target-dose application ratio of conventional neurohormonal antagonist therapy were compared between HFOC and non-HFOC patients at 1 year, as well as 1-year prognosis (all-cause mortality, all-cause rehospitalisation, rehospitalisation for AHF and the composite endpoint of 1-year all-cause mortality and all-cause rehospitalisation). HFOC and non-HFOC patients were propensity-score matched in a 1:1 ratio.

Prognostic indicators were also tested after PSM. The independent influencing factors of 1-year all-cause mortality and 1-year all-cause rehospitalisation were also examined.

5 RESULTS

5.1 In-hospital therapy-optimisation of patients hospitalised for HFrEF

5.1.1 Patient characteristics

Two hundred and thirty-eight patients were included in the analysis. Seventy-five per cent of the cohort was male, the median age was 66 (55–73) years. Ischaemic origin was identified in 40%. Thirty per cent of the patients had a "de novo" diagnosis of HF, and 42% of the cohort had previously been hospitalised for HF. The median duration of hospitalisation was 20 (12–27) days; after discharge, 53% of the patients were followed at our HF Outpatient Clinic. The median left ventricular ejection fraction (LVEF) was 25 (20–30) %. Elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) level at admission (6243 (2719–12167) pg/mL) and the high burden of comorbidities (among others, eGFR < 60 mL/min/1.73m^2: 55%, diabetes: 41%, hypertension: 61%, atrial fibrillation/fibrillation: 48%) indicate the severity of the examined patient cohort. 92% of the total cohort had ≥ 1 comorbidities, while 61% had ≥ 3 comorbidities.

At hospital admission, 58% of the patient cohort received ACEi/ARB, ARNI was applied in 10%, 69% had βB, 61% had MRA

medication, while 3% of them received SGLT2i dapa- or empagliflozin with the indication of diabetes.

5.1.2 GDMT at hospital discharge

At hospital discharge, a significantly ($p<0.050$) larger proportion of patients received RASi (69% vs. 89% [admission vs. discharge respectively]; ACEi/ARB: 58% vs. 70%; ARNI: 10% vs. 19%), βB (69% vs. 85%) and MRA (61% vs. 95%) medication. Consequently, a more significant proportion of patients received TT at discharge (43% vs. 77%, $p<0.001$). Even though SGLT2i-s were not included yet in the pillars of HFrEF therapy in the main part of the data collection period, the application rate of dapagliflozin and empagliflozin also increased (3% vs. 11%, $p<0.001$). The frequency of QT also increased (2% vs. 11%) ($p<0.001$).

Regarding target doses – as defined in the 2021 ESC HF GLs –, 25% of the patients received target doses of RASi- (ACEi/ARB: 26%, ARNI: 22%), 27% of βB-, and 69% of MRA medication (proportions referring only to the patients on each medication). Only a small proportion of patients on TT (8%) and QT (12%) received the recommended target doses of all medications (proportions referring only to the patients on each medication).

5.1.3 The predictive factors of TT application at hospital discharge

Based on the multivariate logistic regression analysis, older age, longer duration of hospitalisation, higher NT-proBNP level at hospital admission, lower eGFR values, and the presence of diabetes were the negative independent influencing factors of the discharge application of TT.

5.1.4 The applicability of novel HFrEF medications (ARNI, SGLT2i, and vericiguat)

From the ARNI-naive patient subgroup (n = 193), based on the applicability criteria of the 2021 ESC HF GLs (eGFR ≥ 30 mL/min/1.73m^2: 82%, systolic blood pressure [SBP] ≥ 90 mmHg: 94%), sacubitril/valsartan could have been applied in 79% of the patients. Regarding the whole patient cohort – those already on ARNI therapy and ARNI-naive patients –, 83% would have been suitable for sacubitril/valsartan. Regarding the SGLT2i-naive subgroup (n = 211), dapa-/empagliflozin could have been initiated in 81% of them based on the applicability criteria of the 2021 ESC HF GLs (eGFR ≥ 20 mL/min/1.73m^2: 93%, SBP ≥ 95 mmHg: 86%). As for the whole patient cohort – those already on SGLT2i therapy and

SGLT2i-naive patients –, 84% would have been suitable for empa-/dapagliflozin medication. Sixty-eight per cent of our patients would have been suitable for vericiguat therapy considering the randomisation criteria of the VICTORIA trial (LVEF < 45%: 100%, SBP ≥ 100 mmHg: 78%, eGFR ≥ 15 mL/min/1.73m^2: 97%, NT-proBNP ≥ 1000 pg/mL and ≥ 1600 pg/mL in case of atrial fibrillation: 89%, New York Heart Association [NYHA] II-IV functional class: 100%, hospitalisation due to HF within six months: 100%).

5.2 The role of kidney dysfunction in the therapy-optimisation and prognosis of HFrEF patients

5.2.1 Patient characteristics

Data from a cohort of 247 patients (75% male, median age 66 (56-74) years) were analysed. Thirty-two per cent of them were diagnosed as "de novo" HFrEF patients, while 40% of the cohort had been hospitalised for HF previously. Forty-five per cent of the patients were followed up at an HF Outpatient Clinic after discharge. Forty-six per cent of the patients were found to have HFrEF – at least partly – due to ischaemic aetiology. Severely abnormal median LVEF (25 (20-30) %), considerably elevated NT-proBNP at admission (6531 (3350-11994) pg/mL), and frequent comorbidities

(diabetes: 40%, hypertension: 63%, atrial fibrillation/flutter: 46%, prehospital diagnosed CKD: 20%, regular dialysis: 1%) characterised the examined patient population.

Based on eGFR values measured at discharge, 53% of the patients had eGFR < 60 mL/min/1.73m^2. The proportions of patients included in the kidney dysfunction groups were as follows: ≥ 90 mL/min/1.73m^2: 15%, 60-89 mL/min/1.73m^2: 32%, 45-59 mL/min/1.73m^2: 20%, 30-44 mL/min/1.73m^2: 21%, < 30 mL/min/1.73m^2: 12%.

At hospital admission, 66% of the patients were on RASi (at target doses of RASi: 21%), 68% on βB (at target doses of βB: 25%), 58% on MRA therapy (at target doses of MRA: 24%), while 42% of them were receiving TT (at target doses of TT: 6%). Fifteen per cent had an implantable cardioverter-defibrillator (ICD) without cardiac resynchronization therapy (CRT), and 11% had a cardiac resynchronisation therapy pacemaker (CRT-P)/ cardiac resynchronisation therapy with defibrillator (CRT-D) at admission.

Even though median eGFR slightly but significantly worsened among the whole cohort during 1-year FUP (eGFR: 61 (41-77) vs. 60 (43-79) vs. 55 (38-66) mL/min/1.73m^2, p<0.001; admission vs. discharge vs. 1 year; based on data of 180 patients having eGFR measured at all three time points), the proportion of patients with the most severe kidney dysfunction categories did not increase.

5.2.2 Complex neurohormonal antagonist therapy according to kidney dysfunction

Combined TT was applied in 77% of the patient cohort at hospital discharge (RASi: 89% [ACEi/ARB: 72%, ARNI: 17%], βB: 85%, MRA: 95%). Ten per cent of them received SGLT2i medication. At 1 year, of the 191 patients still alive, 73% were on TT (RASi: 85% [ACEi/ARB: 62%, ARNI: 23%], βB: 89%, MRA: 83%).

In the whole spectrum of kidney dysfunction categories, neurohormonal antagonist therapy could have been implemented in a remarkable share of patients. However, the presence of more severe kidney dysfunction undoubtedly led to a significantly lower application rate of TT at hospital discharge (92%, 88%, 80%, 73%, 31%, $p<0.001$; in eGFR ≥ 90, 60-89, 45-59, 30-44, < 30 mL/min/1.73m^2 groups, respectively) as well as at 1 year (81%, 76%, 76%, 68%, 40%, $p=0.033$). At hospital discharge, there was a significant difference in the proportion of patients on RASi, while the ratio of patients on MRA therapy did not differ statistically. Regarding βB application, an unfavourable trend was observed at 1 year, while no differences were seen in the use of RASi, βB or MRA medication.

Regarding the target doses achieved at discharge, less favourable renal function did not modify significantly the proportion of patients at target doses of RASi, βB, and TT. However, more

advanced kidney dysfunction was accompanied by a lower implementation rate of MRA therapy with target doses. At 1 year of FUP, target doses of a RASi could have been achieved more frequently among patients with more favourable kidney function, while no significant differences were seen regarding the other assessed first-line HFrEF pharmacotherapies (βB, MRA), and TT.

Eighteen per cent of the patients experienced a significant decrease in eGFR during the index hospitalisation. It is notable that the proportion of patients on TT (70% vs. 78%, p=0.261; eGFR decline > 15% vs. ≤ 15%) and those at target doses of TT (9% vs. 6%, p=0.437; eGFR decline > 15% vs. ≤ 15%) did not differ significantly between those experiencing/not experiencing in-hospital eGFR decline.

5.2.3 Prognosis of patients with HFrEF according to kidney dysfunction

The 1-year all-cause mortality rate of the total cohort was 23%, while the all-cause rehospitalisation rate was 39%. Cardiovascular rehospitalisation affected 26% of the patients, and 17% of them were rehospitalised for AHF. The presence of more severe kidney dysfunction led to significantly increased 1-year all-cause mortality rates (14%, 15%, 16%, 33%, 48%; p<0.001; eGFR ≥

90, 60-89, 45-59, 30-44, < 30 mL/min/1.73m^2 groups). The 1-year all-cause rehospitalisation rates (30%, 35%, 40%, 43%, 52%, p=0.028) and the rate of rehospitalisation for AHF (8%, 13%, 18%, 20%, 38%, p=0.001) were also significantly higher among patients with more advanced kidney dysfunction. No significant differences were observed in cardiovascular rehospitalisation rates (16%, 23%, 28%, 31%, 38%, p=0.064) across the kidney dysfunction spectrum, even though an unfavourable trend was detected.

5.2.4 Therapy adherence

The level of therapy adherence was remarkably high in the whole cohort at 1 year. Neurohormonal antagonist drug regime was discontinued only in 6-17% of patients at 1 year (RASi: 11%, βB: 6%, MRA: 14%, TT: 17%). Among patients not receiving each medication at hospital discharge, the morbidity and mortality-reducing therapy was only newly introduced in 1-6% during the 1-year FUP, and only in an even smaller proportion of the cohort (0-1%) could therapy have been introduced and titrated to the target dose.

5.2.5 Independent predictors of the implementation of TT at discharge and of the 1-year all-cause mortality

In the multivariate logistic regression analysis, the independent positive predictors of the application of TT at hospital discharge were younger age, lower NT-proBNP level, and absence of diabetes mellitus. Regarding 1-year all-cause mortality, younger age, higher SBP, FUP at HFOC, and TT at discharge were the independent parameters that reduced 1-year mortality.

5.3 The impact of HFOC on the long-term application of GDMT and prognosis in HFrEF

5.3.1 Patient characteristics

A total cohort of 257 patients were involved in our retrospective analysis. Seventy-four per cent of them were male, and the median age was 65 (55–73) years. Forty per cent of the patients had been previously hospitalised for HF, 32% were newly diagnosed ("de novo") HFrEF patients and 45% had at least partly ischaemic aetiology of HF. Median LVEF was 25 (20–30) %. The patient population was characterised by multimorbidity (diabetes mellitus: 40%, hypertension: 62%, atrial fibrillation/flutter: 46%). The proportion of patients with at least 1 comorbidity was 93%, and with

at least 3 comorbidities was 61%. At hospital discharge, 89% of the cohort received RASi therapy (ACEi/ARB: 71%, ARNI: 18%), 85% were on βB-, 95% were on MRA medication, while 77% received TT, while SGLT2i usage was 11%. As for the target doses achieved at hospital discharge, 23% of patients were at target doses of RASi, 22% of βB, 68% of MRA, and 6% of TT. 19% had CRT-P/CRT-D, while 22% had an ICD without CRT. At hospital discharge, 44% of the patients accepted HFOC (n = 114), while 56% (n = 143) rejected it for personal reasons.

Comparing the baseline characteristics of HFOC and non-HFOC patient subgroups, significant deviations were identified in terms of age, the proportion of de novo HFrEF patients and medical and device therapy at discharge. After PSM, 84 patients each were assigned to the HFOC and non-HFOC groups, with no differences in the relevant baseline characteristics and therapy.

5.3.2 The impact of HFOC on the application of GDMT

At 1 year, patients followed up with HFOC received RASi (94% vs. 78%, p=0.007; HFOC vs. non-HFOC group, respectively), MRA (95% vs. 71%, p<0.001), and TT (88% vs. 57%, p<0.001) in significantly larger proportions. HFOC patients benefited from target doses of ARNI (17% vs. 5%, p=0.011), βB (54% vs. 19%, p<0.001), MRA (66% vs. 50%, p=0.028), and TT medication (24% vs. 8%,

p=0.003) in a more favourable proportion. At 1 year, neurohormonal antagonist therapy was discontinued in 2–5% of HFOC patients, significantly less (p<0.001) than in the case of the 10–28% discontinuation rate of the non-HFOC group (RASi: 4% vs. 18%; βB: 2% vs. 10%; MRA: 5% vs. 23%; TT: 5% vs. 28%), suggesting that HFOC had an impact on therapy adherence.

After PSM, the application ratios of RASi (96% vs. 79%, p=0.011), MRA (97% vs. 74%, p<0.001), and TT (91% vs. 66%, p<0.001) remained higher in the HFOC group, while management in HFOC was accompanied by a more favourable application ratio of target doses of βBs (51% vs. 22%, p=0.002) and resulted in favourable trends in terms of the proportion of patients on target doses of RASi-s, MRAs and TT at 1 year.

5.3.3 The impact of HFOC on prognosis

1-year all-cause mortality was 23% in the whole cohort, while all-cause rehospitalisation affected 39%, and rehospitalisation for AHF occurred in 17%. Comparison of the 1-year prognosis in HFOC and non-HFOC subgroups shows that the all-cause mortality rate for patients followed up with HFOC was significantly lower (14% vs. 30%, hazard ratio [HR]=0.412, 95% confidence interval [CI]=0.228–0.744, p=0.003), with fewer all-cause rehospitalisations (34% vs.

43%, HR=0.619, 95% CI=0.410–0.934, p=0.022); consequently, the composite endpoints of all-cause mortality or all-cause rehospitalisation rates were also more favourable (38% vs. 58%, HR=0.520, 95% CI=0.358–0.756, p=0.001). Rehospitalisation for AHF also showed a favourable trend in the case of HFOC management (14% vs. 20%, HR=0.566, 95% CI=0.302–1.061, p=0.076) After PSM, the composite endpoint of 1-year all-cause mortality or all-cause rehospitalisation was significantly more favourable in the case of HFOC, leading to a 37.5% relative-risk reduction (42% vs. 57%, propensity-adjusted HR=0.625, 95% CI=0.401–0.974, p=0.038). When the composite endpoint elements were examined separately concerning the effect of HFOC, nonsignificant favourable trends were observed in 1-year all-cause mortality (17% vs. 28%, propensity-adjusted HR=0.563, 95% CI=0.290–1.095, p=0.090). The frequency of 1-year all-cause rehospitalisation did not differ (37% vs. 42%, propensity-adjusted HR=0.744, 95% CI=0.455–1.216, p=0.238). No significant deviation was seen in terms of the 1-year rehospitalisation for AHF (15% vs. 25%, propensity-adjusted HR=0.522, 95% CI=0.255–1.068, p=0.075).

5.3.4 Independent predictors of 1-year all-cause mortality and all-cause rehospitalisation

In the multivariate Cox regression model, younger age, higher SBP, HFOC and the application of TT influenced favourably 1-year all-cause mortality. The application of TT at hospital discharge significantly reduced the risk of all-cause rehospitalisation at 1 year, while FUP with HFOC was associated with a favourable trend.

6 CONCLUSIONS

HF is still a major public health problem that significantly impacts the affected patients' life expectancy. Their prognosis can only be improved through continuous efforts to improve the implementation and successful optimisation of a complex disease-modifying drug regime.

According to our results, the application of GDMT is possible even in a hospitalised HFrEF patient cohort despite the major burden of significant comorbidities and clinical severity of the real-life population, with high therapy adherence during the FUP period. Our findings show that the majority of HFrEF patients are suitable for new pharmacotherapies (SGLT2i, ARNI, and vericiguat) that can significantly modify favourably the prognosis of the disease and patients' quality of life. Accordingly, awareness of the need for their initiation in daily clinical practice must be raised. Furthermore, our analysis confirmed that therapy optimisation is definitely influenced by several factors (age, the presence of concomitant widespread diseases such as diabetes mellitus and impaired kidney function).

The challenge of the presence of comorbidities is unquestionable in the successful, complex treatment implementation of HFrEF. According to our results, despite the negative impact on GDMT initiation, TT can be introduced and optimised safely in a large proportion of patients with significant kidney dysfunction.

Mortality and rehospitalisation rates among patients with HFrEF with kidney dysfunction are unfavourable, which underlines the importance of introducing the disease-modifying drug therapy of HFrEF in patients at the highest risk.

Finally, HFOC is an essential piece of the puzzle in the optimisation and long-term maintenance of GDMT and is strategically important for reducing morbidity and mortality in HFrEF patients. As shown by the results of our study, HFOC favourably modifies the implemented GDMT and may significantly improve the prognosis by reducing the risk of all-cause mortality and all-cause rehospitalisation by 37.5%, even within the first year of its initiation. Therefore, one should insist on the implementation of HFOC in everyday practice.

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