ASSESSMENT OF THE IMPLEMENTATION OF MEDICAL AND DEVICE THERAPY IN HEART FAILURE WITH REDUCED EJECTION FRACTION

Summary of PhD thesis

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1.1 PUBLICATIONS

1.1.1 Related to the thesis

I. Muk B, Vámos M, Bógyi P, Szabó B, Dékány M, Vágány D, Majoros Zs, Borsányi T, Duray GZ, Kiss RG, Nyolczas N. The impact of serum concentration-guided digoxin therapy on mortality of heart failure patients: A long-term follow-up, propensity-matched cohort study Clin Cardiol 2020 Dec;43(12):1641-1648. doi: 10.1002/clc.23500. Epub 2020 Nov 3.
IF: 2.882

II. Pilecky D, **Muk B**, Majoros Zs, Vágány D, Kósa K, Szabó M, Szögi E, Dékány M, Kiss RG, Nyolczas N. Proportion of Patients Eligible for Cardiac Contractility Modulation: Real-Life Data from a Single- Center Heart Failure Clinic. Cardiology. 2021;146(2):195-200. doi: 10.1159/000512946. Epub 2021 Feb 12. PMID: 33582674
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1.1.2 Not related to the thesis

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 (2022). 2022 Dec 5. doi: 10.1159/000528505.
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Pozsonyi Z, Peskó G, Takács H, Csuka D, Nagy V, Szilágyi Á, Hategan L, **Muk B**, Csányi B, Nyolczas N, Dézsi L, Molnár JM, Csillik A, Révész K, Iványi B, Szabó F, Birtalan K, Masszi T, Arányi Z, Sepp R. (2021) Variant Transthyretin Amyloidosis (ATTRv) in Hungary: First Data on Epidemiology and Clinical Features. Genes (Basel). 2021 Jul 28;12(8):1152. doi: 10.3390/genes12081152. **IF: 4.14**

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799. doi: 10.1002/ejhf.1747. Epub 2020 Feb 5. **IF: 15.534**

Pilecky D, Vámos M, Bógyi P, **Muk B**, Stauder D, Rácz H, Nyolczas N, Duray GZ, Zacher G, Zima E. (2019) Risk of cardiac arrhythmias after electrical accident: a single- center study of 480 patients. Clin Res Cardiol, 108: 901-908.
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Bógyi P, Vámos M, Bári Z, Polgár B, **Muk B**, Nyolczas N, Kiss RG, Duray GZ. (2019) Association of Remote Monitoring With Survival in Heart Failure Patients Undergoing Cardiac Resynchronization Therapy: Retrospective Observational Study. J Med Internet Res, 21: e14142. **IF: 5.034**

Vámos M, Nyolczas N, Bári Z, Bógyi P, **Muk B**, Szabó B, Ancsin B, Kiss RG, Duray GZ. (2018) Refined heart failure detection algorithm for improved clinical reliability of OptiVol alerts in CRT-D recipients. Cardiol J, 25: 236-244.
IF: 1.743

Nyolczas N, Dékány M, **Muk B**, Szabó B. (2017) Combination of Hydralazine and Isosorbide-Dinitrate in the Treatment of Patients with Heart Failure with Reduced Ejection Fraction. Adv Exp Med Biol. Adv Exp Med Biol. 2018;1067:31-45.
IF: 2.126

1.2 BACKGROUND

Heart failure (HF) is a complex clinical syndrome with the presence of typical/atypical symptoms (exempli gratia [e.g.] breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) caused by a structural and/or functional cardiac abnormality.

In light of the definition used in the latest European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure published in 2021, heart failure can be classified into phenotypes using the evaluation of left ventricular ejection fraction (LVEF). In accordance with that, those patients with an LVEF≤40%, most frequently measured by echocardiography following the standards approved in the European Association of Cardiovascular Imaging (EACVI) position paper, hence those with significantly impaired left ventricular (LV) systolic function have a HF with reduced ejection fraction (HFrEF).

HFrEF still represents a deadly disease despite the improvements in its complex disease-modifying drug and device treatment. Although its modern, highly effective therapy has advanced significantly over the last decade, the prognosis of HFrEF, even today, is undoubtedly comparable with the outcomes of several malignant diseases. Therefore, the implementation of all available guidelines' recommended therapeutic possibilities is necessary to improve the prognosis successfully. Even today, the inhibition and modulation of the renin-angiotensin-aldosterone and sympathetic nervous system remain the cornerstone of the pharmacological treatment of HFrEF. Hence angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor-neprilysin inhibitor (ARNI), β-blockers (βB), mineralocorticoid receptor antagonists (MRA) complemented by the sodium-glucose cotransporter-2 inhibitor (SGLT2i) dapagliflozin and empagliflozin represent the first-line therapy for HFrEF due to their significant mortality and morbidity reducing effect.

As for treatment optimization, besides the initiation of the disease-modifying drug regime, the accurate, precise implementation of the available pharmacological options, if it is needed, even the second-line agents, focusing on their potential side effects, indisputably represents the cornerstone of modern care in real-world practice. From this point of view, digoxin's optimal, precise application is an important example.

Digoxin is one of the most well-known historical drugs in the cardiology armamentarium and one of the second-line agents for HFrEF treatment. The first publication regarding its efficacy was dated 1785 by William Withering. Heart failure and atrial fibrillation (AF) represent the main indications for its implementation. However, digoxin has been used widely within the last decades, until nowadays only one randomized controlled trial (RCT) has assessed its impact on the prognosis in HFrEF. In the Digitalis Investigation Group (DIG) study, among HFrEF patients presenting with sinus rhythm (SR), the application of digoxin failed to improve all-cause mortality; however, a significant reduction in hospitalization caused by worsening HF was revealed. After the main publication, several observational studies, post-hoc analyses of RCTs, and meta-analyses have been revealed assessing the impact of digoxin on the prognosis in HF and/or AF. Most of these non-randomized publications verified a potentially harmful effect of digoxin in terms of mortality. In these publications remains the concern that the mortality-increasing effect of digoxin may be connected to the lack of control of serum digoxin concentration (SDC) and consequently elevated SDCs. Furthermore, due to the potentially incomplete adjustment of all the potentially influencing confounders, the observed digoxin-associated mortality increase might be due to the more frequent use of this drug among sicker patients.

Alongside the medical therapy, the proper use of devices such as cardiac resynchronization therapy and/or implantable cardioverter-defibrillator (CRT/ICD) has become an integrated, indispensable part of the complex care of HFrEF.

However, despite the application of the "lege artis" drug and device therapy, the prognosis of the disease is still highly unfavourable. Obviously, the continuous effort to look for new, not yet applied, therapeutic possibilities is essential. Cardiac contractility modulation (CCM) represents a new, promising non-pharmacological modality in the field of heart failure.

The principle of CCM is the endocardial electric stimulation of the myocardium during its refractory period, which enhances cardiac contractility without an increase in oxygen consumption. With the knowledge of the initial positive, encouraging acute haemodynamic results observed in the effect of CCM therapy, several randomized and non-randomized studies were initiated to assess the long-term impact of this potential therapeutic modality in HF. These studies have shown that CCM can ameliorate exercise tolerance, functional status, and quality of life. In

addition, the effectiveness of CCM was verified in ischemic and non-ischemic cardiomyopathy as well. In the most recent FIX-HF-5C trial, among the randomized 160 patients with LVEF≥25% and ≤45%, sinus rhythm, NYHA functional class III-IV, and QRS<130msec, the implementation of CCM generated a significant improvement at 24 weeks in terms of New York Heart Association (NYHA) functional class, quality of life, and functional capacity. Besides that, a significant amelioration was revealed in the composite of cardiovascular death and HF hospitalizations. However, current evidence suggests that those patients with LVEF below 25% do not appear to benefit from CCM therapy. Based on the aforementioned data, CCM therapy was included in the expert consensus document of ESC Heart Failure Association, considering CCM as a potentially promising therapeutic alternative in heart failure and emphasizing the need for RCTs examining the effect of CCM with a larger number of patients. Despite the increasing evidence regarding CCM, what proportion of patients with HFrEF meet the eligibility criteria for CCM and, accordingly, the ratio of patients who would be eligible for CCM treatment in real-world clinical practice has not yet been investigated.

1.3 AIM

1.3.1 The impact of digoxin therapy on mortality of HFrEF patients

- To assess the impact of serum digoxin concentration (SDC)-guided digoxin therapy on all-cause mortality in the total cohort of HFrEF patients
- To assess the effect of SDC-guided digoxin therapy on all-cause mortality in the propensity-score-matched patient cohort
- To assess the correlation of serum digoxin concentration and all-cause mortality
- To assess the effect of SDC-guided digoxin therapy on all-cause mortality in patients with sinus rhythm and atrial fibrillation
- To assess the effect of SDC-guided digoxin therapy on all-cause mortality in new digoxin users

1.3.2 The eligibility for cardiac contractility modulation

- To estimate what proportion of HFrEF patients could be eligible for CCM based on the inclusion criteria of the FIX-HF-5C trial

1.4 PATIENTS AND METHODS

1.4.1 The impact of digoxin therapy on mortality of HFrEF patients

1.4.1.1 Patient population

Data from consecutive HFrEF patients managed at the heart failure outpatient clinic (HFOC) of the Medical Centre of Hungarian Defence Forces between 01/01/2007 and 31/12/2017 were collected retrospectively. In addition, demographic data and clinical information were gathered from outpatient records.

Patients were considered to suffer from HFrEF if the left ventricular ejection fraction (LVEF) was <40%. LVEF was measured by echocardiography using the biplane Simpson method.

Patients were classified as digoxin users if digoxin was administered at the time of the initiation of HFOC care and digoxin therapy was applied without interruption during the follow-up period. Patients who received digoxin at the time of referral, but digoxin therapy was discontinued afterward during the follow-up period were excluded from the study. Patients were considered to be new digoxin users if digoxin was initiated at the first visit at the HFOC. Patients who did not receive digoxin at baseline, but digoxin treatment was introduced during the follow-up period were excluded from the study. Patients were considered to be non-digoxin users if digoxin was not used and not started at baseline and during follow-up.

Digoxin initial dosing was calculated with a standardized method. Afterward SDC was measured every three months, and the dose was adjusted according to it. The goal therapeutic range of SDC was 0.5-0.9ng/mL. SDC samples were usually taken after 4-6 hours of oral administration. During follow-up, we made every effort to apply guideline-recommended therapy to every patient. The study complies with the ethical guidelines of the Declaration of Helsinki.

1.4.1.2 Study end points

The outcome measure of this study was time to all-cause mortality. This parameter was compared between digoxin users and non-users across the whole patient population and after propensity score matching. Digoxin users were also divided into three groups based on the maximal SDC measured during follow-up (maxSDC<0.9ng/mL, 0.9≤maxSDC<1.1ng/mL, maxSDC≥1.1ng/mL), and survival

was compared among these subgroups of the propensity-adjusted population. Furthermore, the effect of SDC-guided digoxin therapy on all-cause mortality was assessed in new digoxin users and in patients with AF and SR also in the propensity-adjusted population. Mortality data were obtained from the database of the National Health Insurance Fund of Hungary.

1.4.1.3 Statistical analysis

Statistical analysis was performed using SPSS Statistics software, Version 23.0 (IBM, Armonk, NY) with the R software plug-in (The R Foundation, Version 3.1.0) for propensity score matching.

Continuous variables were expressed as mean ± standard deviations, and differences were compared using 2-sample t tests or the Mann-Whitney U test, as appropriate. Categorical variables were expressed as counts and percentages and differences were assessed with the chi square test.

To assess the effects of SDC-guided digoxin on survival, the Cox proportional hazards regression model was used. The variables included in the multivariate regression analysis are the best-known parameters influencing prognosis in HFrEF. The statistical models were adjusted for potential baseline confounders, including sex, age, etiology of HFrEF, AF, hypertension, diabetes mellitus, NYHA functional class, LVEF, QRS width, heart rate, serum creatinine level, haemoglobin level, βB, ACEi/angiotensin receptor blocker (ARB), MRA, amiodarone, device use. Mortality risk assessment was also repeated among propensity-score-matched patient groups. Patients receiving digoxin were matched in a 1:2 ratio with patients not treated with digoxin using the nearest neighbor matching method with a calliper of 0.2 by applying the baseline characteristics listed above for the multivariate Cox regression. We also assessed the digoxin-associated mortality risk among the following subgroups of the propensity-score adjusted patient cohort: the subgroups defined by maximal SDC measured during follow-up (maxSDC<0.9ng/mL, 0.9≤maxSDC<1.1ng/mL, maxSDC≥1.1ng/mL), patients with SR or AF at baseline, and patients with newly prescribed digoxin at baseline visit.

Survival curves were constructed according to the Kaplan-Meier method and compared with the Cox proportional hazard model and the Wald test for the multivariate analyses. Two-sided p values of <0.05 were considered statistically significant.

1.4.2 The eligibility for cardiac contractility modulation

1.4.2.1 Patient population

Consecutive patients referred to the HF clinic of our tertiary cardiology center (Medical Centre, Hungarian Defence Forces, Budapest, Hungary) between January 01/01/2013 and 31/12/2017 due to HFrEF or heart failure with mildly reduced ejection fraction (HFmrEF) were retrospectively assessed. HFrEF and HFmrEF were defined in accordance with the 2016 ESC HF Guidelines. Relevant clinical, laboratory, echocardiographic, and electrocardiographic parameters were collected at initial visit and after treatment optimization. For patients with HFrEF, guideline-recommended neurohormonal antagonist therapy consisting of β-blocker, ACEi/ARB, and MRA was initiated and uptitrated during follow-up visits to guideline-recommended target doses or maximum tolerated doses. If indicated, ivabradine was used. Attempts were made to minimize doses of diuretics, adjusted at each follow-up visit depending on fluid status and symptoms. Patients who met the indication criteria of current practice guidelines underwent implantation of an ICD or a CRT-pacemaker/defibrillator (CRT-P/D) system. In treatment of patients with initial LVEF between 40 and 49%, we attempted to individually optimize therapy of both cardiovascular and non-cardiovascular comorbidities with a particular focus on hypertension, atrial fibrillation, and coronary artery disease. We included only patients with complete data who were followed up in our outpatient clinic during therapy optimization. LVEF was calculated using Simpson's method.

The enrollment criteria of the FIX-HF-5C study including NYHA class III/IV, 25%≤LVEF≤45%, QRS duration<130msec, and sinus rhythm were applied to identify the proportion of patients eligible for CCM on optimal treatment.

1.4.2.2 Study end points

We assessed the number of patients who could receive CCM as primary device therapy and the proportion of those for whom CCM would be indicated alongside the use of a previously implanted cardiac implantable electronic device. This study was approved by the local Ethical Committee (approval number: KKOO/182-1/2020) and was undertaken in conformity with the Helsinki Declaration.

1.4.2.3 Statistical analysis

Data were obtained from the hospital information system and patient records and were recorded in an anonymized form in a Microsoft Excel 2007 spreadsheet (Microsoft, Redmont, WA, USA). Statistical analysis was performed using the statistical program SPSS 21.0 (IBM, Armonk, NY, USA). The calculated values for categorical variables are represented as percentages, while continuous variables are represented by their means and standard deviations. To compare variables before and after therapy optimization, the McMahon test was used in the case of categorical variables and the paired t test with continuous variables. A 2-sided p value <0.05 was considered statistically significant.

1.5 RESULTS

1.5.1 The impact of digoxin therapy on mortality of HFrEF patients

1.5.1.1 Patient characteristics

From the total cohort (580 patients), in 185 patients, digoxin was applied at the time of their first visit to the HFOC. As expected, digoxin users suffered more often from AF than non-digoxin users (41.1% vs. 21.3%; $p<0.001$), had more decreased ejection fraction (26.4±6.5% vs. 28.0±6.6%; $p=0.003$) and had higher baseline heart rate (89.0±20.0bpm vs. 85.1±19.2bpm; $p=0.026$). In addition, ischemic etiology (50.1% vs. 40.0%; $p=0.023$) was more frequent among non-digoxin users. There was also a significant difference between the two groups regarding baseline device use; significantly more digoxin-treated patients had a previously implanted ICD or CRT-P/D system as opposed to non-users (13.0% vs. 7.6%; $p=0.038$). In terms of drug treatment implemented at baseline, just the minority of patients received the guideline-recommended therapy of HFrEF. Most evaluated patients were referred to our HFOC by secondary care physicians and general practitioners. Consequently, many of them were treatment naïve or undertreated at the time of referrals. In 40.2% of patients a βB-, in 40.3% an ACEi/ARB-, and in 36.7% an MRA was implemented. After the treatment optimization period of three to six months, the proportion of

patients receiving the neurohormonal antagonists increased significantly. In the total cohort, the utilization of βB and ACEi/ARB was also 88.4%, while MRA was used in 57.6%. It has to be underscored that the proportion of patients on target doses of these disease-modifying agents also augmented remarkably (46.7% of βB-treated and 41.5% of ACEi/ARB-treated patients), which results were significantly favourable than observed in the recently published registry data. The mean daily digoxin dose during follow-up was 111±50μg. During the study period, the angiotensin receptor-neprilysin inhibitor application was still not available. After applying a 1:2 propensity score matching protocol, a cohort of 477 patients was assembled (180 digoxin-treated and 297 digoxin-not-treated patients). In comparison with pre-matched patients, those in the matched cohort were well balanced with respect to the collected baseline risk factors with a standard mean difference of less than 20 %; however patients on digoxin therapy had higher incidence of atrial fibrillation (39.4% versus 27.9%, p=0.009).

1.5.2 The effect of serum digoxin concentration - guided digoxin therapy on all-cause mortality

1.5.2.1 The effect of SDC-guided digoxin therapy on all-cause mortality in the total cohort

During the mean follow-up of 7.1±4.7 years, from the total cohort, 351 patients (60.5%) died, 131 patients out of 185 digoxin users (70.8%), and 220 patients out of the 395 non-digoxin users (55.7%). The univariate survival analysis of the total cohort revealed that digoxin use was associated with an increased risk of all-cause mortality (Hazard ratio [HR]: 1.453; [95% Confidence Interval - CI -: 1.170-1.804]; p=0.001). However, after adjustment for potential confounders in multivariate Cox regression analysis, baseline digoxin use remained an independent predictor of all-cause mortality (HR: 1.939; [95% CI: 1.512-2.487]; p<0.001).

1.5.2.2 The impact of SDC-guided digoxin therapy on all-cause mortality in the propensity-score-matched patient cohort

In the propensity-score-matched patient cohort 126 patients, out of the 180 digoxin users (70.0%), and 165 patients, out of the 297 non-digoxin users (55.6%) died. The all-cause mortality of digoxin-users was significantly higher than non-users (propensity adjusted HR: 1.430; [95% CI: 1.134-1.804]; p=0.003).

1.5.2.3 Correlation of serum digoxin concentration and all-cause mortality

Those patients who had a maxSDC of between 0.9 and 1.1ng/mL (n=60) and patients with maxSDC≥1.1ng/mL (n=44) had an elevated risk of all-cause mortality as opposed to non-digoxin users (HR: 1.750; [95% CI: 1.257-2.436]; p=0.001 and HR: 1.687; [95% CI: 1.153-2.466]; p=0.007). However, this raised hazard of mortality was not statistically significant in the subgroup of patients with a maxSDC of <0.9ng/mL (n=76) (HR: 1.139; [95% CI: 0.827-1.570]; p=0.426).

1.5.2.4 The effect of SDC-guided digoxin therapy on all-cause mortality in patients with sinus rhythm and atrial fibrillation

When survival was evaluated according to digoxin application in the subgroup of patients with SR at baseline, we confirmed that digoxin use was associated with an increased hazard of mortality (propensity adjusted HR: 1.553; [CI: 1.157-2.084]; p=0.003). This phenomenon was not statistically significant among those having AF at baseline (HR: 1.106; [CI: 0.756-1.619]; p=0.604).

1.5.2.5 The effect of SDC-guided digoxin therapy on all-cause mortality in new digoxin users

When the impact of digoxin was assessed among the 123 new digoxin users in comparison with digoxin non-users, we found that digoxin implementation led to a significantly elevated risk of all-cause mortality (HR: 1.371; [95% CI: 1.062-1.770]; p=0.016).

1.5.3 The eligibility for cardiac contractility modulation

Six hundred forty patients were referred due to HFrEF or HFmrEF and followed up at our HFOC during the study period. Of these 640 patients, 48.1% (n=308) suffered from coronary artery disease, and 28.0% had persistent or permanent atrial fibrillation. The mean LVEF in the whole patient cohort was 29.0±7.9% at baseline, and 63.1% of patients had a QRS width<130msec. At the time of the first presentation, 43.9% of patients received a β-blocker, 38.1% an ACEi/ARB, and 38.3% a mineralocorticoid receptor antagonist. Among patients with HFrEF (n=579), the proportion of patients on β-blocker, ACEi/ARB, MRA was significantly increased through individual optimization of medical therapy to 88.4, 96.5, and 57.0%, respectively. The guideline-recommended target dose of β-blockers and ACEi/ARBs was achieved in 46.8 and 36.8% of patients with HFrEF. After treatment optimization, 424 patients (66.3%) were found to have improved at least one NYHA class, therefore, the proportion of severely symptomatic patients (NYHA III–IV) decreased from 77.0% to 18.6% ($p<0.001$). Mean LVEF increased significantly to 36.3±9.9% ($p<0.001$). The proportion of patients with 25%≤LVEF≤45% increased from 69.7% (n=446) to 73.3% (n=469) ($p<0.001$).

We found that the eligibility criteria for CCM therapy based on the FIX-HF-5C study were fulfilled for 23.0% (n=147) of our patient population at baseline and 5.2% (n=33) after treatment optimization. Ten of the 33 potential CCM candidates would receive CCM as a second device in addition to a pacemaker or implantable cardioverter defibrillator implanted previously.

1.6 DISCUSSION

1.6.1 The impact of digoxin therapy on mortality of HFrEF patients

1.6.1.1 Main findings

In this real-life, community-based cohort of optimally treated HFrEF patients, we confirmed that SDC-guided digoxin therapy was associated with increased all-cause mortality, especially with SDC≥0.9ng/mL. Furthermore, all-cause mortality

was significantly elevated in patients with SR and in new digoxin users in comparison with patients not treated with digoxin.

1.6.1.2 Serum-concentration-guided digoxin therapy

The narrow therapeutic window for the use of digitalis glycosides is well known. However, most publications that demonstrated an elevated mortality risk associated with digoxin did not report data about daily digoxin dose and/or serum levels. Even in the studies that reported such information, serum digoxin measurements were not performed in a systematic fashion. For example, in the DIG trial, SDC was measured only at four weeks and one year after the start of the study, while digoxin toxicity was followed only by signs and symptoms at four months, and every four months thereafter. In a study by Freeman et al. comprising 2891 newly diagnosed HFrEF patients, SDC was measured at all in 70% of patients and was measured just once in 27% of patients. Consequently, the lack of regular SDC control and/or higher SDC may have contributed to the adverse mortality effect of digoxin observed in these trials.

Our retrospective study demonstrates that even with an extremely close monitoring strategy, which was performed systematically in every patient, it was only possible to maintain SDC below 0.9ng/mL in 42% of patients during the entire follow-up. This may be partly due to the pharmacokinetics of digoxin (it eliminates mainly through the kidneys), and the fact that the renal function of HFrEF patients is typically impaired. It, therefore, appears to be reasonable to use digitoxin instead of digoxin in HFrEF because of its hepatic elimination. Evidence regarding the effects of digitoxin on morbidity and mortality or data about its safe therapeutic range is even more limited. In a single-centre study of 1020 ICD recipients, treatment with digoxin or digitoxin was associated with similarly increased mortality compared to digitalis non-user. The ongoing Digitoxin to improve outcomes in patients with advanced chronic heart failure (DIGIT-HF) trial will hopefully be able to clarify the place of digitoxin in therapy for HFrEF. This trial investigates the hypothesis that digitoxin – at serum concentrations in the lower therapeutic range – reduces mortality and morbidity in patients with HFrEF with or without AF.

1.6.1.3 Correlation of serum digoxin concentrations and mortality

A post-hoc analysis of the DIG trial has raised the concern that high SDC (≥1.2ng/mL) could lead to an increase in all-cause and cardiovascular mortality, and favourable digoxin effects are only expected in patients with SDC between 0.5 and 0.8ng/mL. In the recently published post-hoc analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, baseline digoxin implementation was not associated with an increased risk of mortality compared to patients not treated with digoxin. However, a 56% increase in relative mortality risk was demonstrated in patients with an SDC≥1.2ng/mL compared to those not on digoxin. The study also found a linear correlation between SDC and all-cause mortality: an 0.5ng/mL increase in SDC increased mortality by 19%. This phenomenon was also verified in our analysis; serum digoxin concentration was correlated with a 14% higher adjusted hazard of death for each 0.5ng/mL increase. In opposition to the above-mentioned post-hoc analysis of the ARISTOTLE trial, we confirmed an increase in mortality risk across the entire patient cohort before and after propensity score matching. This difference may be explained by the variability in patient populations: in the ARISTOTLE trial, every patient had AF, 37.4% of whom suffered from concomitant HF, while in our study, every patient had HFrEF, and only 27.6% suffered from AF. In the ARISTOTLE study, among patients whose digoxin level was measured at baseline, 76.0% had SDC levels below 0.9ng/mL. In comparison, only 42% of our patient population had maxSCD<0.9ng/mL.

In contrast to the DIG study, we could not identify a favourable mortality effect in patients with maxSDC<0.9ng/mL. This may be explained by the fact that there were significant differences between our patient population and those cohorts (for example, we included patients with AF also, in contrast to the DIG trial). Moreover, digoxin users had more advanced HF with lower left ventricular ejection fraction in our cohort, and the proportion of patients with hypertension or diabetes was higher compared to the DIG trial. Finally, it should also be noted that the morbidity- and mortality-reducing drug and device therapies were applied in higher proportion and dose in our patients than they were used in the DIG trial, which also could have modified the possible deleterious effects of digoxin.

1.6.1.4 The effect of digoxin on mortality in patients with atrial fibrillation and sinus rhythm

The results of studies that evaluated the effect of digoxin on the mortality of HFrEF patients in SR and AF are quite controversial. In a meta-analysis published by Vamos et al., a substantially increased risk of death was associated with digoxin in both HF and AF, although the relative risk of mortality was higher in patients with AF (23% vs. 11%). The post-hoc analysis of the ARISTOTLE trial also demonstrated a direct correlation between serum digoxin level and overall mortality in patients with AF, which was consistent in patients with HF. However, Hallberg et al. – using data from the Registry of Information and Knowledge about Swedish Heart Intensive Care Admissions – did not find a difference in one-year digoxin-associated mortality among patients with HF with or without AF. Our study demonstrated increased mortality in digoxin-treated HFrEF patients in SR but not in patients with AF. The Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (RATE-AF) trial assessing the effect of digoxin in permanent AF and HF, verified an amelioration in the N-terminal (NT)-pro hormone B-type natriuretic peptide (BNP) (NT-proBNP) level, and in the modified European Heart Rhythm Association (EHRA) class in the effect of digoxin in comparison with bisoprolol. In addition, the application of digoxin in the RATE-AF trial was associated with fewer adverse events as opposed to the implementation of bisoprolol.

1.6.1.5 The effect of digoxin on mortality in new digoxin users

Parallelly to the post-hoc analysis of the ARISTOTLE trial and other previous reports, we also verified a significant elevation in all-cause mortality in new digoxin users as opposed to patients not treated with digoxin (HR: 1.371; [95% CI: 1.062-1.770]). Although this result may be underpowered because of the limited number of new digoxin users, this type of analysis appears to be particularly important since it reduces the survival bias that is present in most of the observational studies.

1.6.2 The eligibility for cardiac contractility modulation

In a real-life cohort of patients we found that the eligibility criteria for CCM therapy based on the FIX-HF-5C study were fulfilled in 23.0% of our patient population before and in 5.2% after treatment optimization.

The basis of CCM is a non-excitatory, relatively high voltage (~7.5V), long-duration (~20 millisecond), biphasic electrical signal delivered during the absolute refractory period of the ventricle. The device (Optimizer system - Impulse Dynamics, Orangeburg, NY) is typically implanted in the right pectoral region and is connected to two standard pacemaker leads that are placed through venous access into the right ventricular septum at a distance of at least 2 cm from each other. The beneficial effects of CCM manifest at the molecular, cellular, and extracellular level. Positive changes in the remodelling of intracellular Ca^{2+} regulatory proteins and increasing sensitivity of myofilaments to Ca^{2+} appear to be the most important molecular changes, leading to improvement not only in regional but also in global LV contractility. The three prospective randomized trials proved that CCM in addition to optimized medical therapy (OMT) is effective at reducing symptoms and improving exercise capacity and quality of life in patients with NYHA class III-IV, $25\% \leq LVEF \leq 45\%$, QRS<130msec, and sinus rhythm versus OMT alone. Additionally, the most recent FIX-HF-5C study showed an approximately 50% reduction in the composite end point of cardiovascular death and HF hospitalizations at six months. The clinical effectiveness of CCM is most convincing in patients with LVEF between 35-45%, while patients with LVEF below 25% do not appear to benefit from this therapy. Due to the invasive nature and costs of this therapy, careful patient selection and thorough follow-up are necessary.

To the best of our knowledge, our analysis is the first report to describe an assessment of the proportion of patients who would be eligible for CCM therapy based on current evidence in a real-world patient population. We found that 5.2% (n=33) of our patients met the indication criteria, and about one-third (n=10) of them would be eligible for a CCM as a second device additional to another cardiac implantable electronic device implanted previously. In the analysis of Dulai et al. 5.1% of the examined cohort of hospitalized HF patients were suitable for CCM therapy. A previous review article from Abi-Samra estimated that 79% of patients with NYHA II-III and LVEF<35% could be eligible for CCM. The reason for this

apparent discrepancy in eligibility is that this rough estimation ignored some important eligibility criteria derived from the results of former RCTs.

The relatively small proportion of eligible patients in our patient cohort is due to several reasons. The main cause is that through accurate optimization of guideline-recommended therapy the proportion of highly symptomatic patients was reduced and LVEF increased significantly. The fact that the proportion of HFrEF patients receiving a target dose of neurohormonal antagonist therapy was fairly large (higher than reported in the ESC Heart Failure Long-Term Registry) can explain this impressive improvement in NYHA class and LVEF. The relatively large proportion of CRT recipients could also have contributed to clinical improvement. Of course, our single-centre data cannot be automatically extrapolated to the whole chronic heart failure (CHF) patient population, although we found that the baseline characteristics and prevalence of comorbidities in our cohort were very similar to those of the Hungarian and other large multicentric heart failure registry data. The mean age was 61.3 years in our patient cohort, 63 years in Qualify Registry, 64.4 years in Hungarian Heart Failure Registry and 66 years in ESC HF Long-term Registry in chronic heart failure patients. The proportion of males was 76% in the Biology study to tailored treatment in chronic heart failure (BIOSTAT-CHF) and Evidence based treatment - heart failure (EVITA) Registries, 74% in Qualify Registry, 72.3% in Hungarian Heart Failure Registry and 76.1% in our patient population. The incidence of diabetes was 38.7%, 34% and 34.4% and incidence of hypertension was 75.8%, 64% and 72.5% in EVITA and Qualify Registries and in our patient cohort. Therefore, a similar eligibility proportion can be assumed in other heart failure patient populations. Our eligibility data are also in line with patient selection data from the FIX-HF-5C study, where only about one-third of patients who had signed informed consent passed baseline testing and underwent randomization. There are presently several gaps in the evidence about CCM. If these are filled, the proportion of patients eligible for CCM is likely to increase in the future. First, in the above-mentioned RCTs it was predominantly patients with NYHA class III-IV who were included; there is a lack of evidence concerning whether NYHA II patients would also benefit from this therapy. We found that by ignoring this criterion the number of suitable patients increased to 13.3%. It is also important to note that in single-centre studies and in CCM-REG the proportion of NYHA II patients was 8-20%, but this finding should be verified through further prospective studies. Second, since the previous generation CCM

signal delivery algorithm required the sequential intracardiac sensing of a P wave and ventricular signal, patients with permanent or persistent atrial fibrillation were excluded from the randomized trials. The new-generation Optimizer Smart does not require the implantation of an atrial lead and contains an algorithm which also delivers a signal during atrial fibrillation. As approximately half of all patients with HF develop atrial fibrillation at some point, further studies are required to assess the effect of CCM in this patient population. Third, while the effects of CCM therapy have primarily been tested in patients with narrow or mildly prolonged QRS (<130msec), two studies with low patient numbers evaluated the efficacy of CCM among patients who had a wide QRS and were non-responders to CRT. The authors found an improvement in quality of life and exercise tolerance, similar to the results of earlier randomized trials. Since about 20-40% of patients who receive CRT do not obtain benefit from CRT, CCM could be an alternative therapeutic option for them. Finally, it is also important to mention that although the proportion of patients eligible for CCM was relatively small in our patient cohort, thus regarding the wide prevalence of disease this may mean a high total number of CCM candidates in the whole population.

1.7 CONCLUSIONS

1.7.1 The impact of digoxin therapy on mortality of HFrEF patients

Digoxin represents one of the oldest drugs in the armamentarium of the medical treatment of HFrEF. Although it has been relegated to the background of the pharmaceutical therapy of HFrEF within the last decade as a result of several observational studies and non-randomized recent data, the proportion of patients on digoxin in HFrEF is still relevant.

As a consequence of that and in the knowledge of the potentially harmful effect of digoxin frequently caused by the unfavourable high serum concentration and the lack of the regularly measured SDC, in our analysis the impact of SDC-guided digoxin therapy on mortality among HFrEF patients followed at a HFOC was evaluated. According to the results of our retrospective, single-centre study, serum-concentration-guided digoxin therapy was associated with increased all-cause mortality in optimally treated HFrEF patients, especially with SDC≥0.9 ng/mL. It has

to be highlighted that the harmful effect of digoxin was not observed among patients with SDC less than 0.9 ng/mL. With a precise, regularly SDC-measured digoxin implementation, it was possible to maintain the SDC in the therapeutic range only in 40% of our patient cohort. It can be highlighted as well that the safe use of digoxin which does not lead to unfavourable outcomes in HFrEF, is hardly feasible.

1.7.1.1 Limitations

However, in our non-randomized patient cohort analysis, we aimed to minimize potential confounding factors by carefully adjusting our data along important patient characteristics potentially responsible for worse outcomes using two different statistical methods (i.e., adjusted multivariate Cox regression and propensity score matching), residual bias cannot be excluded, as this was pointed by Aguirre Dávila et al. in a recently published post-hoc analysis of the DIG trial. The observed neutral effect of digoxin in the subgroup of patients with SDC<0.9ng/mL on mortality should be interpreted carefully, hence this group represents a small number of patients and has limited statistical power. The data collection process for our patient cohort started in 2007. Since then, there have been changes in the guideline recommendations regarding the pharmacological and device treatment of HFrEF. These changes may have modified the mortality effect of digoxin. Our single-centre patient population consisted of only Caucasians. Accordingly, the study's results do not necessarily apply to patients outside this group.

1.7.2 The eligibility for cardiac contractility modulation

The initiation of the device therapy, in case of the persisting severely reduced LVEF in spite of the optimized guideline-directed medical therapy, plays a crucial role, a mandatory step in the complex care of symptomatic HFrEF patients. In this continuously developing field of the treatment of HFrEF, besides the implantation of an ICD and/or CRT, CCM seems to be an interesting, promising new modality. Within the last years, several small, randomized, or observational studies revealed a potential beneficial effect of CCM as an add-on therapy in HFrEF. In the most recent FIX-HF-5C trial, a significant improvement with CCM at 24 weeks was verified regarding the quality of life and functional capacity. Moreover, a significant

amelioration was confirmed in the composite of cardiovascular death and HF hospitalizations. However, it is not known what proportion of the HFrEF patients are suitable for this therapy in the everyday practice. Our short-term single-centre cohort study confirmed that nearly 5% of patients with HFrEF after treatment optimization would be eligible for CCM after completing the inclusion criteria of the FIX-HF-5C trial. Moreover, we found that by including all symptomatic HFrEF patients, the proportion of suitable patients increased to 13.3%.

1.7.2.1 Limitations

Besides the single-centre character of the study, the main limitation of our work is that none of the patients received either sacubitril/valsartan or SGLT2i-s in our patient population because these drugs were unavailable during the study period in Hungary. The further limitation was the short follow-up period of the current analysis involving only the period of treatment optimization of 3-6 months, and due to the progressive nature of the disease it is likely that the clinical state of some patients would have worsened over time despite optimized medical therapy, thereby becoming candidates for CCM.

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