Rationale, Design, and Methodology of the APOLLON trial: A comprehensive, Observational registry of heart failure with mid-range and preserved ejection fraction

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OBJECTIVE: Although almost half of chronic heart failure (HF) patients have mid-range (HFmrEF) and preserved left-ventricular ejection fraction (HFpEF), no studies have been carried out with these patients in our country. This study aims to determine the demographic characteristics and current status of the clinical background of HFmrEF and HFpEF patients in a multicenter trial.

METHODS: A comprehensive, Observational registry of heart failure with mid-range and preserved ejection fraction (APOLLON) trial will be an observational, multicenter, and noninterventional study conducted in Turkey. The study population will include 1065 patients from 12 sites in Turkey. All data will be collected at one point in time and the current clinical practice will be evaluated (ClinicalTrials.gov number NCT03026114).

RESULTS: We will enroll all consecutive patients admitted to the cardiology clinics who were at least 18 years of age and had New York Heart Association class II, III, or IV HF, elevated brain natriuretic peptide levels within the last 30 days, and an left ventricular ejection fraction (LVEF) of at least 40%. Patients fulfilling the exclusion criteria will not be included in the study. Patients will be stratified into two categories according to LVEF: mid-range EF (HFmrEF, LVEF 40%-49%) and preserved EF (HFpEF, LVEF ≥50%). Regional quota sampling will be performed to ensure that the sample was representative of the Turkish population. Demographic, lifestyle, medical, and therapeutic data will be collected by this specific survey.

CONCLUSION: The APOLLON trial will be the largest and most comprehensive study in Turkey evaluating HF patients with a LVEF ≥40% and will also be the first study to specifically analyze the recently designated HFmrEF category. (Anatol J Cardiol 2018; 19: 311-8)

KEYWORDS: demographic characteristics, heart failure with mid-range ejection fraction, heart failure with preserved ejection fraction
Introduction

Heart failure (HF) is categorized by a reduced left ventricular ejection fraction (LVEF) (HFrEF, LVEF <40%) or by a preserved LVEF (HFpEF, LVEF ≥50%). However, current guidelines recognize HF with mid-range ejection fraction (HFmrEF, LVEF 40%-49%) as an entity distinct from HFrEF and HFpEF (1). Nearly half of the population with HF worldwide has HFpEF or HFmrEF (2-4), and these conditions have become a major public health problem because their prevalence rate increases by 1% every year (5), with rates of cardiovascular mortality and morbidity similar to those seen in HFrEF (6-8). Clinical profile, presentation, and pathophysiology of HFpEF and HFmrEF are heterogeneous and their management remains controversial. In contrast to HFrEF, no specific therapy has been shown to significantly improve the outcome of HFpEF or HFmrEF, which may be explained by heterogeneity in the underlying pathophysiological mechanisms and frequently associated co-morbidities in these populations (6). However, most of the HFpEF and HFmrEF studies have been conducted in western countries, and limited information is available in other regions of the world. The epidemiology and management of HFpfEF and HFmrEF could be quite different in developing countries, such as Turkey, from that in western countries with respect to the ethnic background and etiology. The heart failure prevalence and predictors in Turkey (HAPPY) trial was the largest study in Turkey conducted on HF patients (9). This study included 4650 randomly selected residents aged ≥35 years to determine the prevalence of HF in Turkey, based on echocardiography and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Results of the HAPPY study have shown that the prevalences of HF and asymptomatic left ventricular dysfunction were higher in Turkey than those in western countries, despite a younger Turkish population. However, this study has some methodological limitations such as underuse of echocardiography and lack of current standard definitions of HFpEF (9). The Turkish registry for diagnosis and treatment of acute heart failure (TAKTIK) study was a prospective national survey of 36 medical centers across Turkey (10). A total of 588 patients who were hospitalized with acute HF were enrolled. Echocardiographic data was available for 88% of patients, and the mean LVEF was 33%±13%. Preserved LVEF, defined as LVEF ≥40%, was present in 20% of patients (10). However, demographic or clinical characteristics of HFpEF patients were not specifically analyzed in the TAKTIK study. Due to scarce data on HFpEF and no data on HFmrEF in our country, the APOLLON study aimed to provide comprehensive data including detailed clinical characteristics and medication usage on HFpEF and HFmrEF.

The results of the APOLLON trial will provide critical knowledge for understanding the disease entity, optimizing patient management, and designing clinical trials in HFpEF and HFmrEF patients.

Methods

Study design and setting

The APOLLON trial was designed as a multicenter, noninterventional (observational) study to evaluate the demographic characteristics of HFmrEF and HFpEF patients. The study will be performed by hospital-based cardiologists who regularly treat HF patients. Under the leadership of Muğla Sıtkı Koçman University Cardiology Department, 13 centers were enrolled in the study. The sample sizes of the regions included in the study are shown in Figure 1. The names of the coordinators and researchers are shown in Table 1.

The study will not stipulate any diagnostic or treatment procedures. The study was approved by the Institutional Review Board or Local Ethics Committee (Muğla Sıtkı Koçman University) and registered at ClinicalTrials.gov (NCT03026114). Sample size is calculated based on the assumption that 50% of HF patients have HFpEF or HFmrEF. Power calculation is based on a two-sided test, with a power of 0.80, and with a significance level of 0.05; the required sample size was 1065. From March 31, 2018, to June 30, 2018, a total of 1065 patients who presented to the outpatient cardiology clinics with New York Heart Association class II, III, or IV HF sign and/or symptoms will be enrolled in the study at 12 sites across the country. The 1st Geography Congress in Turkey, held in Ankara in 1941, divided Turkey into seven separate regions based on climate, human habitat, agricultural diversity, and topography. To ensure adequate geographic diversity in patients included in the APOLLON study, the number of patients enrolled from each region will be proportional to the population of that region. The geographical distribution of hospitals across the country and the overall profile of the participating cardiology institutions will be representative of the national setting of cardiovascular care in Turkey. Participants will be enrolled during a routine ambulatory visit. The geographical distribution of hospitals across the country and the overall profile of the participating cardiology institutions will be representative of the national setting of cardiovascular care in Turkey.

Eligibility criteria

To qualify for documentation in the study, adult outpatients must fulfill all of the following eligibility criteria:

- Must have documented HF criteria
- Age ≥18 years
- LVEF ≤50% or LVEF >50%
- HFpEF, HFmrEF, or HFrEF
- HF diagnosis within the past 6 months
- HF symptoms for ≥3 months
- NYHA class II, III, or IV
- HF hospitalization within the past 12 months
- HF medications and therapy adherence
- Consent to participate

Figure 1. Geographic distribution of the APOLLON study patients in Turkey (number of patients in each region are shown in parentheses)
1. Patients aged ≥18 years at the time of enrollment;
2. Patients willing to participate and provide written informed;
3. Patients with a LVEF ≥40%;
4. Signs and symptoms of HF are defined in Table 2. One symptom must be present at the time of screening and one sign must be present in the last 12 months. Heart failure eligibility should be carefully monitored and documented in the subject's medical records;
5. Brain natriuretic peptide (BNP) level in the last 30 days >35 pg/mL or N-terminal pro-B-type natriuretic peptide (NT-proBNP) level >125 pg/mL.

### Exclusion criteria

1. Patients with a LVEF <40%;
2. Significant chronic pulmonary disease according to the investigator;
3. Primary hemodynamically significant uncorrected valvular heart disease, obstructive or regurgitant;
4. Patients with any history of surgically corrected heart valve diseases (e.g., mechanical or bioprosthetic heart valves);
5. Myocardial infarction, stroke, or coronary artery bypass graft surgery in the past 90 days;
6. Percutaneous coronary intervention or pacemaker implantation in the past 30 days;
7. Heart transplant recipient;
8. Known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial constriction;
9. Congenital heart disease;
10. Cor pulmonale;
11. Pregnancy.

### Measurements

Table 3 provides a summary of the items that appeared in the APOLLON survey questionnaire. The demographic, clinical, and other objective data will be collected for each participant at the visit and will include the following:

1. Age, sex, smoking history, level of education, place of residence (rural or urban), body mass index, and alcohol use;
2. Previous therapies or interventions to treat HF;
3. Concomitant medications;
4. Vital signs and laboratory tests including B-type natriuretic peptide (BNP) and/or NT-proBNP levels;
5. Signs and symptoms at presentation (e.g., paroxysmal nocturnal dyspnea, orthopnea, dyspnea on exertion, rales, ankle edema, neck-vein distention, pleural effusion, pulmonary edema, appetite loss, cardiac murmur, third heart sound, ankle swelling,

Less typical
Nocturnal cough
Wheezing
Bloating
Loss of appetite
Confusion
Depression
Palpitations
Dizziness
Syncope
Bendopnea

Less specific
Weight gain (>2 kg/week)
Weight loss or cachexia
Cardiac murmur
Peripheral edema
Pulmonary crepitations
Tachycardia
Tachypnoea
Hepatomegaly
Ascites
Oliguria

Table 3. Summary of the APOLLON survey questionnaire

| Number of patients | 1065 |
|--------------------|------|
| Study type         | Multicenter, cross-sectional, observational |
| Patient population | HfPEF and HFmrEF patients who presented to the outpatient cardiology clinics |
| Demographic information | Gender, Age, Body mass index, Smoking history, Place of residence (rural or urban), Level of education, Alcohol use, Hospitalization history of heart failure in the last 1 year |
| Patient's complaint | Breathlessness (NYHA class), Orthopnea, Paroxysmal nocturnal dyspnea, Reduced exercise tolerance, Bendopnea, Palpitations, Fatigue, tiredness, increased time to recover after exercise, Ankle swelling, Nocturnal cough, Syncope, Dizziness, Chest pain |
| Physical examination findings | Blood pressure, Heart rate, Jugular venous pressure, Cardiac murmur, Third heart sound (gallop rhythm), Peripheral edema (ankle, sacral, scrotal), Pulmonary crepitations, Tachypnoea, ECG abnormality, Ascites, Tissue wasting (cachexia) |
| Laboratory data | B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide Fasting blood glucose |
and New York Heart Association functional classification on admission; 6. Comorbidities (e.g., hypertension, diabetes, atrial fibrillation, coronary artery disease, prior stroke, renal failure, chronic obstructive pulmonary disease, and obstructive sleep apnea syndrome); 7. Transthoracic echocardiography and 12-lead ECG results at rest for all patients; 

**Definition of HF in the study population**

HF is defined as the presence of signs and/or symptoms of congestive heart failure, elevated BNP levels (>35 pg/mL) or NT-proBNP levels (>125 pg/mL).

All patients will be screened by transthoracic echocardiography, and LVEF will be assessed using the conventional apical two- and four-chamber views and the modified Simpson’s method. Patients will classified according to the new terminology of the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF as HFrEF (LVEF ≥50%) and HFmrEF (LVEF 40%–49%) (1). For the determination of HFrEF and HFmrEF, at least one additional echocardiographic criterion including relevant structural heart disease or diastolic dysfunction is required (Fig. 2). Key structural alterations were accepted as a left atrial volume index (LAVI) >34 mL/m² or a left ventricular mass index (LVMI) ≥115 g/m² for males and ≥95 g/m² for females. Key diastolic dysfunction criteria were accepted an E/e’ ≥13 and a mean e’ septal and lateral wall <9 cm/s.

| Comorbidities      | Medication                                  |
|--------------------|---------------------------------------------|
| Atrial fibrillation| Angiotensin converting enzyme-inhibitor    |
| Hypertension       | Angiotensin receptor blocker                |
| Diabetes mellitus  | B blocker                                   |
| Renal failure      | Aldosterone receptor antagonist             |
| Obstructive sleep  | Ivabradine                                   |
| apnea syndrome     | Amiodarone                                   |
| Hyperlipidemia     | Calcium channel blockers                    |
| History of myocardial infarction |-loop diuretics                             |
| Coronary artery disease |Thiazide diuretics                     |
| Cardiac pacemaker  | Nitrate                                     |
| Peripheral artery  | Antiplatelet therapy                        |
| disease            | Anticoagulant therapy                       |
| Cerebrovascular    | ARNI                                        |
| disease            | Nonsteroidal anti-inflammatory drugs        |
| Chronic obstructive| Oral antidiabetic drugs                     |
| pulmonary disease  | Insulin                                     |
| Liver disease      |                                             |
| Depression         |                                             |
| Malignancy         |                                             |

HFpEF - Heart failure with preserved left ventricular ejection fraction, HFmrEF - heart failure with mid-range ejection fraction, NYHA - New York Heart Association, ARNI - Angiotensin II Receptor Blocker Neprilysin Inhibitor.

| Echocardiography findings | Table 3. Cont. |
|---------------------------|----------------|
| e’ (a mean septal and lateral wall) | Blood urea nitrogen |
| E/e’                      | Serum creatinine |
| LV end diastolic diameter | Serum sodium    |
| LV end systolic diameter  | Serum potassium |
| Interventricular septum diameter | Serum calcium |
| LV posterior wall diameter | Serum uric acid |
| Left atrium volume index  | Ferritin        |
| Pulmonary artery systolic pressure | C-reactive protein |
| Mitral regurgitation      | B blocker       |
| Mitral stenosis           | Aldosterone receptor antagonist             |
| Aortic stenosis           | Ivabradine                               |
| Aortic regurgitation      | Amiodarone                                |
| Tricuspid regurgitation   | Calcium channel blockers                  |
| Atrial fibrillation       | Nitrate                                    |
| Hypertension              | Antiplatelet therapy                      |
| Diabetes mellitus         | Anticoagulant therapy                     |
| Renal failure             | ARNI                                       |
| Obstructive sleep apnea syndrome | Nonsteroidal anti-inflammatory drugs    |
| Hyperlipidemia            | Oral antidiabetic drugs                    |
| History of myocardial infarction | Insulin                                 |
| Coronary artery disease   |                                             |
| Cardiac pacemaker         |                                             |
| Peripheral artery disease |                                             |
| Cerebrovascular disease   |                                             |
| Chronic obstructive       |                                             |
| pulmonary disease         |                                             |
| Liver disease             |                                             |
| Depression                |                                             |
| Malignancy                |                                             |

and New York Heart Association functional classification on admission;
Statistical analyses

Summary statistics will be provided as percentages (%) or as mean with standard deviations (SD). Baseline continuous variables will be presented as mean±SD or median and interquartile range, depending on the distribution of the data; categorical data will be presented as counts and percentages. We will compare the categorical variables using the χ² test and the continuous variables using the t-test or the Mann–Whitney U-test, as appropriate. Univariate and multiple regression analyses will be used to calculate odds ratio and 95% confidence interval. Analyses are and will be performed with SPSS system software (version 24.0 or higher).

Discussion

Approximately 50% of all HF patients exhibit a reduced LVEF termed HFrEF and the others may be classified into HFmrEF or HFrpEF (1). Data from the US and Europe suggest that the demographic characteristics, symptom profile, comorbidities, laboratory values, and outcomes of HFrEF and HFrpEF patients may differ from those of HFrEF patients (11, 12). However, to our knowledge, there have been no clinical trials examining patients’ clinical profiles and management with HFmrEF or HFrpEF in Turkey. Therefore, the APOLLON trial aimed to (1) demonstrate the current status of the clinical background of HFmrEF and HFrEF patients, (2) determine standard clinical practice on HF management, and (3) analyze the appropriateness of medical therapy in HFmrEF and HFrpEF patients in a large, multicenter, and observational trial.

Several high-quality epidemiologic studies have shown that HFrpEF patients are predominantly elderly, more likely to be females, and have a high prevalence of comorbidities such as hypertension, diabetes mellitus, atrial fibrillation, and coronary artery disease (5, 8). These studies have also demonstrated that HFrpEF is an emerging epidemic and survival with HFrpEF is poor, especially after hospitalization for HF.

After the release of 2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF, numerous studies have been performed to identify demographic and clinical characteristics of HFmrEF patients and to investigate whether these patients are characterized by diverse features, different comorbid conditions, and distinct therapeutic needs compared with HFrpEF or HFrEF patients (11-13). Recent studies have shown that the prevalence of HFmrEF in the HF population is between 13% and 24% (14-16).

Get With The Guidelines (GWTG) registry revealed the data of >40,000 hospitalized HF patients and showed that 47% of the patients had HFrEF, 14% had HFmrEF, and 39% had HFrEF (17). HFmrEF patients had characteristics more similar to HFrEF patients than HFrEF patients, and treatment for HFmrEF patients was in a pattern that resembled treatment for HFrpEF patients (17). HFrEF patients had slightly increased mortality at 1 year (37.5%) compared with HFmrEF (35.1%) and HFrpEF (35.6%) patients (17). In another study of hospitalized HF patients, HFmrEF patients had mortality rates of 21.3% at 1 year, which was intermediate between those of HFrpEF (22.2%) and HFrEF (25.5%) patients (8). Farmakis et al. (18) published the results of the Acute Heart Failure Global Registry of Standard Treatment trial that included 4953 patients hospitalized for HF in nine countries. This study showed that 811 (24.9%) patients had HFmrEF and 748 (23.0%) HFrpEF. The majority of HFmrEF patients were males (64.9%), and 29.3% of them aged >75 years. The proportion of elderly and female patients was higher in these patients compared to HFrEF patients. However, the number of elderly and female patients was lower in HFmrEF patients compared to patients with HFrpEF. Compared with HFrEF and HFrpEF patients, HFmrEF patients had a higher prevalence of hypertension and dyslipidemia, an intermediate prevalence of coronary artery disease, and a lower prevalence of chronic renal disease (18). The results of current observational and population-based studies suggested that HFrEF and HFmrEF patients show higher percentages of ischemic heart disease and idiopathic dilated cardiomyopathy, and hypertensive heart disease and valvular heart disease are the more common etiologies in HFrpEF (11, 19). The Swedish Heart Failure registry showed that the rates of ischemic heart disease were 60% for HFrEF, 61% for HFmrEF, and 52% for HFrpEF (20).

The ESC Heart Failure Long-term Registry revealed the differences in medical therapy in these three groups of HF patients (19). Use of beta-blockers and angiotensin-converting enzyme inhibitors was approximately 90% in both HFrEF and HFmrEF compared with approximately 75% in HFrpEF. Use of mineralocorticoid receptor antagonists was approximately 70% in HFrEF, 55% in HFmrEF, and 35% in HFrpEF. Ivabradine was prescribed to approximately 10% of HFrEF and HFmrEF patients and 5% of HFrpEF patients.

Inspite of the general belief that HFmrEF patients are considered to be the “middle child of HF” (21) or transition of HFrEF to HFrpEF (and vice versa), at least in some studies, HFmrEF seems to be more similar to HFrEF in terms of ischemic etiology, biomarker profile, and response to treatment (22).

In summary, although the ‘intermediate’ clinical profile of HFmrEF between HFrEF and HFrpEF would support the conclusion that HFmrEF is a distinct clinical entity, there is no data about HFmrEF or HFrpEF in our country. The APOLLON study will be the first study in HFrpEF and HFmrEF patients in Turkey. The findings of this study will provide important real world evidence as well as potentially providing a better understanding of the burden of HFrpEF and HFmrEF and the variability in disease management in individual units.

Study limitations

The APOLLON study is a limited cross-sectional survey that will provide a snapshot of HFmrEF or HFrpEF. Therefore, it will not be possible to observe the course of the disease, and informa-
tion regarding prognosis data will be limited. Another limitation is that the coverage of the study is limited to outpatient cardiology clinics. Lastly, we have excluded patients with normal BNP or NT-proBNP levels. However, recent studies have shown that up to 30% of patients with confirmed HfPEF have normal natriuretic peptide levels (23-25).

**Conclusion**

This study is designed to evaluate current demographic, clinical, echocardiographic, and biomarker characteristics and clinical practice in HfPEF and HfMREF patients. The results of the APOLLON study will provide direction for future research and guide the clinical management of these patients.

**Conflict of interest:** None declared.

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**References**

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al.; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18: 891-975.
2. Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Predictors of inhospital mortality in pa-
tients hospitalized for heart failure: insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). J Am Coll Cardiol 2008; 52: 347-56.
3. Adams Jr KF, Fonarow GC, Egerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005; 149: 209-16.
4. Sato N, Kajimoto K, Asai K, Mizuno M, Minami Y, Nagashima M, et al. Acute decompensated heart failure syndromes (ATTEND) reg-

istry. A prospective observational multicenter cohort study: rationale, design and preliminary data. Am Heart J 2010; 159: 949-55.e1.
5. Owman TE, Hodge DO, Hergerms RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with pre-
served ejection fraction. N Engl J Med 2006; 355: 251-9.
6. Tribouilloy C, Rusinaru D, Mahjoub H, Soulière V, Lévy F, Peltier M, et al. Prognosis of heart failure with preserved ejection fraction: a 5-year prospective population-based study. Eur Heart J 2008; 29: 339-47.
7. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al. Relation of disease pathogenesis and risk factors to heart fail-
ure with preserved or reduced ejection fraction: insights from the Framingham heart study of the national heart, lung and blood institu-
t. Circulation 2009; 119: 3070-7.
8. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haozi A, et al. Outcome of heart failure with preserved ejection fraction in a popula-
tion-based study. N Engl J Med 2006; 355: 260-9.
9. Değeretkin M, Erol C, Ergene O, Tokgözüloğlu L, Aksoy M, Erol MK, et al. Heart failure prevalence and predictors in Turkey: HAPPY study. Turk Kardiyl Dern Ars 2012; 40: 298-308.
10. Eren M, Zoghi M, Tuncer M, Cevuşoğlu Y, Demirbaş R, Şahin M, et al.; TAKTIK Investigators. Turkish registry for diagnosis and treatment of acute heart failure: TAKTIK study. Turk Kardiyl Dern Ars 2016; 44: 637-46.
11. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail 2017; 19: 1624-34.
12. Hsu JJ, Ziaean B, Fonarow GC. Heart Failure With Mid-Range (Borderline) Ejection Fraction: Clinical Implications and Future Directions. JACC Heart Fail 2017; 5: 763-71.
13. Rastogi A, Novak E, Platts AE, Mann DL. Epidemiology, pathophys-
ology and clinical outcomes for heart failure patients with a mid-
range ejection fraction. Eur J Heart Fail 2017; 19: 1597-605.
14. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF, et al. Precipitating clinical factors, heart failure characteriza-
tion, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. JACC Heart Fail 2016; 4: 464-72.
15. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauuchi T, Onose T, et al. Characterization of heart failure patients with mid-range left ven-
tricular ejection fraction-a report from the CHART-2 Study. Eur J Heart Fail 2017; 19: 1258-69.
16. Coles AH, Tisminetzky M, Yarzebski J, Lessard D, Gore JM, Dar-
ling CE, et al. Magnitude of and prognostic factors associated with 1-year mortality after hospital discharge for acute decompensated heart failure based on ejection fraction findings. J Am Heart Assoc 2015; 4: pii: e002303.
17. Cheng RK, Cox M, Neely ML, Heidenreich PA, Bhatt DL, Eapen ZJ, et al. Outcomes in patients with heart failure with preserved, bor-
derline, and reduced ejection fraction in the Medicare population. Am Heart J 2014; 168: 721-30.
18. Farmakis D, Simitsis P, Bistola V, Tripkioskiadis I, Ikonomidis I, Kat-
sanos S, et al. Acute heart failure with mid-range left ventricular ejection fraction: clinical profile, in-hospital management, and short-term outcome. Clin Res Cardiol 2017; 106: 359-68.
19. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2017; 19: 1574-85.
20. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, et al. Significance of Ischemic Heart Disease in Patients With Heart Failure and Preserved, Midrange, and Reduced Ejection Fraction: A Nationwide Cohort Study. Circ Heart Fail 2017; 10. pii: e003875.

21. Lam CS, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40-50%). Eur J Heart Fail 2014; 16: 1049-55.

22. Nauta JF, Hummel YM, van Melle JP, van der Meer P, Lam CSP, Poni-kowski P, et al. What have we learned about heart failure with mid-range ejection fraction one year after its introduction? Eur J Heart Fail 2017; 19: 1569-73.

23. Anjan VY, Loftus TM, Burke MA, Akhter N, Fonarow GC, Gheorghiade M, et al. Prevalence, clinical phenotype, and outcomes associated with normal B-type natriuretic peptide levels in heart failure with preserved ejection fraction. Am J Cardiol 2012; 110: 870-6.

24. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, et al. Systolic and diastolic heart failure in the community. JAMA 2006; 296: 2209-16.

25. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, et al. Patho-physiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002; 288: 2144-50.