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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Abstract

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

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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 population (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 HFpEF 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 α 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:

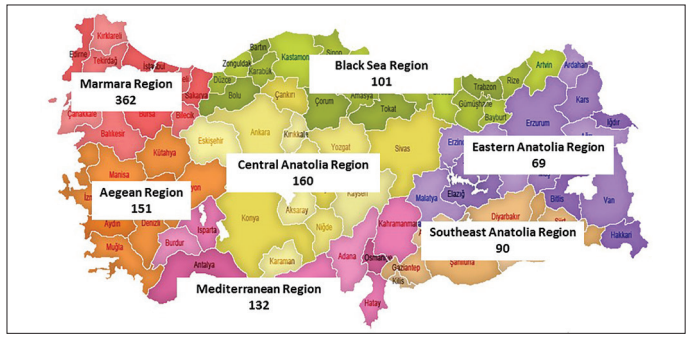

Figure 1. Geographic distribution of the APOLLON study patients in Turkey (number of patients in each region are shown in parentheses)

Table 1. The names of the participating researchers and centers with patient number in the APOLLON trial

City	Researcher (Name, Surname)	Center	Patient Number
Muğla	Bülent Özlek	Muğla Sıtkı Koçman University Training and Research Hospital (Coordinating Center)	151
Muğla	Murat Biteker	Muğla Sıtkı Koçman University Training and Research Hospital (Coordinating Center)	
Muğla	Eda Özlek	Muğla Sıtkı Koçman University Training and Research Hospital (Coordinating Center)	
Muğla	Volkan Doğan	Muğla Sıtkı Koçman University Training and Research Hospital (Coordinating Center)	
Muğla	Oğuzhan Çelik	Muğla Sıtkı Koçman University Training and Research Hospital (Coordinating Center)	
Muğla	Cem Çil	Muğla Sıtkı Koçman University Training and Research Hospital (Coordinating Center)	
Muğla	Özcan Başaran	Muğla Sıtkı Koçman University Training and Research Hospital (Coordinating Center)	
İstanbul 1	Hicaz Zencirkıran Ağuş	Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital	115
İstanbul 1	Serkan Kahraman	Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital	85
İstanbul 1	Samet Sevinç	Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital	72
İstanbul 2	Altuğ Ösken	Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital	90
Ankara	Veysel Ozan Tanık	Dışkapı Yıldırım Beyazıt Training and Research Hospital	90
Eskişehir	Kadir Uğur Mert	Eskişehir Osmangazi University Faculty of Medicine	25
Kayseri	Erkan Demirci	Kayseri Training and Research Hospital	15
Kayseri	Engin Dondurmacı	Kayseri Training and Research Hospital	15
Kırıkkale	Yunus Çelik	Kırıkkale Yüksek İhtisas Hospital	15
Kahramanmaraş	Mehmet Tekinalp	Kahramanmaraş Necip Fazıl City Hospital	132
Çorum	Lütfü Bekar	Hitit University Çorum Erol Olçok Training and Research Hospital	50
Zonguldak	Mustafa Ozan Çakır	Bülent Ecevit Universiy Medical Faculty	51
Kars	İbrahim Rencüzoğulları	Kafkas University Medical Faculty	69
Şanlıurfa	Bedri Caner Kaya	Mehmet Akif İnan Training and Research Hospital	68
Adıyaman	Hakan Tibilli	Adıyaman University, Training and Research Hospital	22
Total			1065

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;

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;

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Table 2. Common signs and symptoms of heart failure

Symptoms	Signs
Typical	**More Specific**
Breathlessness	Elevated jugular venous pressure
Orthopnoea	Hepatojugular reflux
Paroxysmal nocturnal dyspnea	Third heart sound
Reduced exercise tolerance	
Fatigue, tiredness	
Ankle swelling	
Less typical	**Less specific**
Nocturnal cough	Weight gain (>2 kg/week)
Wheezing	Weight loss or cachexia
Bloated feeling	Cardiac murmur
Loss of appetite	Peripheral edema
Confusion	Pulmonary crepitations
Depression	Tachycardia
Palpitations	Tachypnoea
Dizziness	Hepatomegaly
Syncope	Ascites
Bendopnea	Oliguria

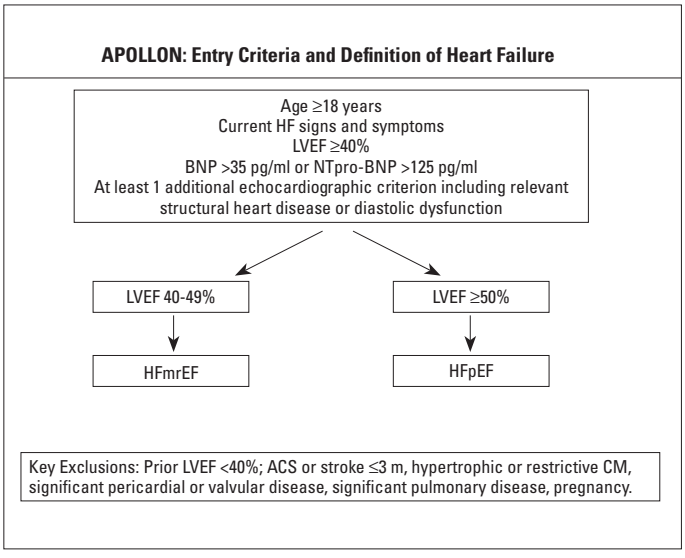

Figure 2. Flow diagram illustrating patients meeting entry criteria and definition of heart failure

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, orthopnoea, dyspnea on exertion, rales, ankle edema, neck-vein distention, pleural effusion, pulmonary edema, appetite loss, cardiac murmur, third heart sound,

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)
	Orthopnoea
	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

Table 3. Cont.

	Blood urea nitrogen
	Serum creatinine
	Serum sodium
	Sorum potassium
	Serum calcium
	Serum uric acid
	Thyrotrophin-stimulating hormone
	Hemoglobin
	Leukocyte
	C-reactive protein
	Ferritin
Echocardiography findings	e' (a mean septal and lateral wall)
	E/e'
	LV end diastolic diameter
	LV end sistolic diameter
	Interventricular septum diameter
	LV posterior wall diameter
	Left atrium volume index
	Pulmonary artery systolic pressure
	Mitral regurgitation
	Mitral stenosis
	Aortic stenosis
	Aortic regurgitation
	Tricuspid regurgitation
Comorbidities	Atrial fibrillation
	Hypertension
	Diabetes mellitus
	Renal failure
	Obstructive sleep apnea syndrome
	Hyperlipidemia
	History of myocardial infarction
	Coronary artery disease
	Cardiac pacemaker
	Peripheral artery disease
	Cerebrovascular disease
	Chronic obstructive
	pulmonary disease
	Liver disease
	Depression
	Malignancy
Medication	Angiotensin converting
	enzyme-inhibitor
	Angiotensin receptor blocker
	B blocker
	Aldosterone receptor antagonist
	Ivabradine
	Amiodarone
	Propafenone
	Calcium channel blockers
	Digoxin
	Statin
	Loop diuretics
	Thiazide diuretics
	Nitrate
	Antiplatelet therapy
	Anticoagulant therapy
	ARNI
	Nonsteroidal anti-inflammatory drugs
	Oral antidiabetic drugs
	Insulin

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

and New York Heart Association functional classification on admission);

6. Comorbidities (e.g., hypertension, diabetes, atrial fibrillation, coronary artery disesase, 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 HFpEF (LVEF ≥50%) and HFmrEF (LVEF 40%-–49%) (1). For the determination of HFpEF 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/m^2 or a left ventricular mass index (LVMI) ≥115 g/m^2 for males and ≥95 g/m^2 for females. Key diastolic dysfunction criteria were accepted an E/e′ ≥13 and a mean e' septal and lateral wall <9 cm/s.

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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 χ^2 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 HFpEF (1). Data from the US and Europe suggest that the demographic characteristics, symptom profile, comorbidities, laboratory values, and outcomes of HFmrEF and HFpEF 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 HFpEF in Turkey. Therefore, the APOLLON trial aimed to (1) demonstrate the current status of the clinical background of HFmrEF and HFpEF patients, (2) determine standard clinical practice on HF management, and (3) analyze the appropriateness of medical therapy in HFmrEF and HFpEF patients in a large, multicenter, and observational trial.

Several high-quality epidemiologic studies have shown that HFpEF 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 HFpEF is an emerging epidemic and survival with HFpEF 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 chracteristics of HFmrEF patients and to investigate whether these patients are characterized by diverse features, different comorbid conditions, and distinct therapeutic needs compared with HFpEF 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 HFpEF, 14% had HFmrEF, and 39% had HFrEF (17). HFmrEF patients had characteristics more similar to HFpEF patients than HFrEF patients, and treatment for HFmrEF patients was in a pattern that resembled treatment for HFpEF patients (17). HFrEF patients had slightly increased mortality at 1 year (37.5%) compared with HFmrEF (35.1%) and HFpEF (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 HFpEF (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%) HFpEF. 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 HFpEF. Compared with HFrEF and HFpEF 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 HFpEF (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 HFpEF (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 HFpEF. Use of mineralocorticoid receptor antagonists was approximately 70% in HFrEF, 55% in HFmrEF, and 35% in HFpEF. Ivabradine was prescribed to approximately 10% of HFrEF and HFmrEF patients and 5% of HFpEF patients.

Inspite of the general belief that HFmrEF patients are considered to be the "middle child of HF" (21) or transition of HFrEF to HFpEF (and vise 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 HFpEF would support the conclusion that HFmrEF is a distinct clinical entity, there is no data about HFmrEF or HFpEF in our country. The APOLLON study will be the first study in HFpEF 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 HFpEF 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 HFpEF. 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.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – B.Ö., E.Ö., O.Ç., C.Ç., V.D., Ö.B., M.B.; Design – B.Ö., E.Ö., O.Ç., C.Ç., V.D., Ö.B.; Supervision – B.Ö., E.Ö., O.Ç., C.Ç., V.D., Ö.B.; Fundings – H.Z.A., L.B., M.O.Ç., E.Demirci; Materials – B.Ö., V.D., M.T., H.Z.A., S.K., A.Ö., İ.R., V.O.T., L.B., M.O.Ç., B.C.K., H.T., Y.Ç., S.S., E. Dondurmacı; Data collection &/or processing – B.Ö., E.Ö., O.Ç., C.Ç., V.D., M.T., H.Z.A., S.K., A.Ö., İ.R., V.O.T., L.B., M.O.Ç., B.C.K., H.T., Y.Ç., Ö.B., K.U.M., S.S., E. Demirci, E. Dondurmacı, M.B.; Analysis &/or interpretation – S.K., A.Ö., İ.R., V.O.T., B.C.K., H.T., K.U.M., S.S., E. Demirci; Literature search – B.Ö., E.Ö., K.U.M., E. Dondurmacı; Writing – B.Ö., E.Ö., O.Ç., C.Ç., V.D., M.B.; Critical review – B.Ö., M.B.

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. [CrossRef]
2. Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Predictors of inhospital mortality in patients 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. [CrossRef]
3. Adams Jr KF, Fonarow GC, Emerman 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. [CrossRef]
4. Sato N, Kajimoto K, Asai K, Mizuno M, Minami Y, Nagashima M, et al. Acute decompensated heart failure syndromes (ATTEND) registry. A prospective observational multicenter cohort study: rationale, design and preliminary data. Am Heart J 2010; 159: 949-55.e1.
5. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006; 355: 251-9. [CrossRef]
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. [CrossRef]
7. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham heart study of the national heart, lung and blood institute. Circulation 2009; 119: 3070-7. [CrossRef]
8. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006; 355: 260-9. [CrossRef]
9. Değertekin M, Erol C, Ergene O, Tokgözoğlu L, Aksoy M, Erol MK, et al. Heart failure prevalence and predictors in Turkey: HAPPY study. Turk Kardiyol Dern Ars 2012; 40: 298-308. [CrossRef]
10. Eren M, Zoghi M, Tuncer M, Çavuşoğlu Y, Demirbağ R, Şahin M, et al.; TAKTIK Investigators. Turkish registry for diagnosis and treatment of acute heart failure: TAKTIK study. Turk Kardiyol Dern Ars 2016; 44: 637-46. [CrossRef]
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, Ziaeian B, Fonarow GC. Heart Failure With Mid-Range (Borderline) Ejection Fraction: Clinical Implications and Future Directions. JACC Heart Fail 2017; 5: 763-71. [CrossRef]
13. Rastogi A, Novak E, Platts AE, Mann DL. Epidemiology, pathophysiology and clinical outcomes for heart failure patients with a mid-range ejection fraction. Eur J Heart Fail 2017; 19: 1597-605. [CrossRef]
14. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF, et al. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. JACC Heart Fail 2016; 4: 464-72. [CrossRef]
15. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study. Eur J Heart Fail 2017; 19: 1258-69. [CrossRef]
16. Coles AH, Tisminetzky M, Yarzebski J, Lessard D, Gore JM, Darling 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. [CrossRef]
17. Cheng RK, Cox M, Neely ML, Heidenreich PA, Bhatt DL, Eapen ZJ, et al. Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicare population. Am Heart J 2014; 168: 721-30. [CrossRef]
18. Farmakis D, Simitsis P, Bistola V, Triposkiadis F, Ikonomidis I, Katsanos 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. [CrossRef]
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. [CrossRef]

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DOI:10.14744/AnatolJCardiol.2018.95595

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. [CrossRef]
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. [CrossRef]
22. Nauta JF, Hummel YM, van Melle JP, van der Meer P, Lam CSP, Ponikowski 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. [CrossRef]
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. [CrossRef]
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. [CrossRef]