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Clinical Management Strategies of Cardiologists in Heart Failure with Reduced Ejection Fraction in Türkiye

Türkiye'de Azalmış Ejeksiyon Fraksiyonlu Kalp Yetersizliğinde Kardiyologların Klinik Yönetim Stratejileri

ABSTRACT

Objective: Integrating heart failure (HF) guideline recommendations into clinical practice takes time and is often suboptimal in real-life settings. Physician-related factors may be significant barriers to the adoption of these guidelines. This survey aims to assess the current opinions of cardiologists practicing in Türkiye regarding the management of heart failure with reduced ejection fraction (HFrEF).

Methods: The survey comprised 22 questions and was published on the SurveyMonkey platform.

Results: A total of 177 cardiologists (mean age: 39.5 years; 73.3% male) participated in the survey. Of these, 38.7% worked in a training and research hospital, and 10.2% were specialists in HF. The threshold EF value to define HFrEF was ≤ 40% for 80.1% of the cardiologists. While 52.6% of physicians considered angiotensin receptor-neprilysin inhibitor (ARNi) treatment the most effective medication for HF, 62.7% would initiate HF treatment with an angiotensin-converting enzyme inhibitor (ACEi) instead of ARNi due to reimbursement and cost issues. More than half of the cardiologists (52.3%) stated that adding another class of HF medication is more important than up-titrating those already prescribed. Although 69.5% of the study participants indicated prescribing all four classes of HF medications during the initial hospitalization is feasible, most cardiologists preferred a sequential approach starting with ACEi/ARNi, followed by beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 inhibitors (SGLT2i).

Conclusion: This survey highlights significant discrepancies between guideline recommendations and the real-life clinical practice of cardiologists in Türkiye. These results suggest that there is a need for organized action by healthcare providers to improve the implementation of guideline recommendations.

Keywords: Guideline, heart failure, recommendation, treatment

ÖZET

Amaç: Kalp yetersizliği (KY) kılavuz önerilerinin klinik pratikte uygulanması zaman almaktadır ve genellikle gerçek yaşam şartlarında optimal düzeyde uygulanmamaktadır. Bu zorluğun önemli nedenlerinden biri hekim ile ilişkili faktörlerdir. Bu anket çalışmasının amacı, Türkiye'deki kardiyoloji uzmanlarının düşük ejeksiyon fraksiyonlu kalp yetersizliği (DEF-KY) tedavi tercihlerini belirlemektir.

Yöntem: Anket çalışması 22 sorudan oluşmaktadır. Bu sorular, SurveyMonkey üzerinden yayınlanmış ve anket katılım linki birçok sosyal medya aracı üzerinden hekimlere ulaştırılmıştır.

Bulgular: Anket çalışmasına Türkiye'de görev yapmakta olan 177 kardiyoloji uzmanı ve asistanı katıldı. Katılımcıların ortalama yaşı 39.5, %73.3'ü erkek, %38.7'si eğitim ve araştırma hastanelerinde görev yapmakta idi ve sadece %10.2'si kendisini KY uzmanı olarak tanımlamaktaydı. Katılımcıların %80.1'i, DEF-KY tanısı için sınır ejeksiyon fraksiyonu değerini %40 olarak kabul ettiklerini belirttiler. Hekimlerin %52.6'sı anjiyotensin reseptör-neprilisin inhibitörü (ARNi) tedavisini "en etkili KY tedavisi" olarak kabul ettiklerini belirtmelerine karşın, %62.7'si ilacın geri ödeme kısıtlılıkları ve fiyatı nedeniyle, DEF-KY tedavisine ARNi yerine anjiyotensin dönüştürücü enzim inhibitörü (ADEi) ile başlamak zorunda kaldıklarını belirttiler. Katılımcıların %52.3'ü tedaviye farklı bir KY ilaç sınıfını eklemenin, halihazırda kullanılan ilaçların dozunu arttırmaktan daha önemli olduğunu belirttiler. Hekimlerin %69.5'i yeni tanı KY hastalarında, hastane yatışı sırasında dört KY ilaç sınıfını aynı anda başlamanın mümkün olduğunu belirttiler. Buna karşın günlük pratiklerinde, sırasıyla ADEi/ARNI, beta-bloker, mineralokortikoid reseptör antagonisti ve sodyum-glukoz ko-transporter 2 inhibitörlerini başladıkları sıralı yaklaşımı daha çok tercih ettiklerini belirttiler.

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Sonuç: Bu anket çalışması, kılavuz önerileri ile gerçek yaşam uygulamaları arasında önemli farklılıklar olduğunu ortaya koymaktadır. Kılavuz önerilerinin, klinik pratikte uygulanabilmesi için sağlık sağlayıcıların gerekli önlemleri almalarına ve düzenlemeleri yapmalarına ihtiyaç vardır.

Anahtar Kelimeler: Kılavuz, kalp yetersizliği, öneri, tedavi

Heart failure (HF) is an escalating health problem, with heart failure with reduced ejection fraction (HFrEF) linked to higher rates of hospitalization and mortality.[1] Guideline-directed medical therapy (GDMT), which includes angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor-neprilysin inhibitor (ARNi), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 inhibitors (SGLT2i), is advocated to lessen the risk of hospitalization and death in patients with HF.[1-3]

While the recommendations of previously published HF guidelines relied on a traditional hierarchical approach to managing HFrEF, the 2023 European Society of Cardiology HF guideline advocates the initiation of all four classes of HF treatments for all patients with HFrEF during the index hospitalization or at an early outpatient visit following hospital discharge.[3] However, registries and observational studies indicate that the implementation of these guideline recommendations into clinical practice takes time and is usually suboptimal in real-life settings.[4,5] In a multicenter registry in Türkiye, 78% of HFrEF patients were prescribed ACEi or ARNi, 90% were prescribed beta-blockers, and only 55% were prescribed MRAs.[4] Moreover, the proportion of patients receiving target doses of HF medications was 24% for ACEi or ARNi, 9% for beta-blockers, and 10% for MRAs in the same registry.[4] The SMYRNA (Prognostic significance of medical therapy in patients with heart failure with reduced ejection fraction) study reported that less than 50% of eligible patients with HFrEF receive triple therapy comprising ACEi or ARNi, beta-blockers, and MRAs in Türkiye.[6]

ABBREVIATIONS

ACC	American College of Cardiology
ACEi	Angiotensin-converting enzyme inhibitor
AHA	American Heart Association
ARNi	Angiotensin receptor-neprilysin inhibitor
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
ESC	European Society of Cardiology
GDMT	Guideline-directed medical therapy
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy
MRAs	Mineralocorticoid receptor antagonists
NT-proBNP	N-terminal pro b-type natriuretic peptide
PARADIGM-HF	Prospective comparison of ARNi with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure
PIONEER-HF	Practical Implementation of Clinical Guidelines Optimized for Effective Reduction of HF-Related Morbidity and Mortality
SGLT2i	Sodium-glucose cotransporter 2 inhibitors
STRONG-HF	Strategy to Reduce Heart Failure Hospitalizations with Intensive Upscaling of Guideline-Directed Medical Therapy
TRANSITION	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
VICTORIA	Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction

The main identified barriers to the implementation of guidelines could be classified as *patient-related factors* (the presence of multiple comorbidities, frailty, and/or advanced age); *healthcare system-related factors* (restriction of access to healthcare services, legislation on reimbursement for medications, and/or cost of medications); and *physician-related factors*.[4,5] *Physician-related factors* including lack of awareness about the HF guidelines, a focus on eliminating symptoms rather than on reducing mortality, fear of side effects, or reluctance and lack of motivation may be the most important barriers to guideline implementation.[4,5] For example, an international web-based survey focusing on the perception and implementation of HF guidelines by physicians reported that the 'historical approach' for HFrEF management remains the preferred approach despite the current recommendations.[7]

According to the data from the Ministry of Health of Türkiye Health Statistics Yearbook-2022, 95,600 specialist physicians are working at 915 public hospitals operated by the Ministry of Health, 572 private hospitals, and 68 university hospitals in Türkiye. Although the proportion of medications covered by the reimbursement criteria of the Social Security Institution in Türkiye was 94.4% in 2022, ARNi treatment is not included within the scope of reimbursement. Similarly, SGTL2i treatment is also not covered by reimbursement for patients with HF except diabetic patients. The reimbursement restrictions pose a critical obstacle to implementing the guidelines for HF by cardiologists.

There is limited data about the perception and implementation of HF guidelines among cardiologists practicing in Türkiye; thus, it is crucial to obtain actual data. The present survey aims to determine the current opinions of cardiologists practicing in Türkiye about the management of HFrEF.

Materials and Methods

The present survey was adapted from an international cardiology survey conducted by Fauvel et al.[7] The survey questions were translated into Turkish, edited by the first author (U.K.), and implemented on SurveyMonkey.com (Momentive, Waterford, NY, USA). The survey material consisted of 22 individual questions (the Turkish version of the survey questions is presented in the Supplementary Table).

The survey was published on the SurveyMonkey platform, and the survey link was posted on several social networks. It was available for one month on the web platform. There were no conflicts of interest to declare upon drafting and implementing this survey. No industry or organizational support was involved at any stage of this process.

The study was conducted in accordance with the principles of the Declaration of Helsinki, and all participants provided written informed consent. This study was approved by the Başkent

University Medical and Health Sciences Ethics Committee (Project No. KA19/58, Approval Number: 94603339-604.01.02/-7720, Date: 25.02.2019).

Continuous variables were expressed as mean ± standard deviation for those normally distributed and median (interquartile range, IQR) for those with skewed distribution. Categorical variables were expressed as percentages. The Student's t-test and Kruskal-Wallis test were used to evaluate group differences for continuous variables, and the chi-squared test for categorical ones. Six pre-specified subgroup analyses were systematically performed: sex (female versus male), age group (≤ 40 years versus > 40 years), HF specialist versus non-specialists, geographic regions, location of practice, and academic ranks. *P* values < 0.05 were considered significant. All statistical analyses were performed using SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Main Characteristics of Study Participants

Overall, 177 cardiologists from seven geographical regions of Türkiye completed the survey between January 22, 2023 and February 22, 2023. The mean time spent to complete the questionnaire was 6.7 minutes, and over 90% of participants answered all questions in the survey.

The main characteristics of the study participants are presented in Table 1. The mean age was 39.5 ± 6.9 years (range: 27-70), and two-thirds of the participants were under 40 years. There was a predominance of male cardiologists (*n* = 127, 73.4%). Most participants resided in the Aegean and Marmara regions (32.4% and 28.3%, respectively) and practiced in training and research hospitals (38.7%). The most common subspecialities were general cardiology (42.0%) and interventional cardiology (35.8%), with only 10.2% of participants being HF specialists.

Table 1. Main Characteristics of the Study Participants (n = 177)

Variables	n	
Age, years	176	39.5 ± 6.9
Age group	176	
≤ 40 years		111 (63.1)
> 40 years		65 (36.9)
Male sex	173	127 (73.4)
Geographic region	173	
Mediterranean		15 (8.7)
Eastern Anatolia		12 (6.9)
Aegean		56 (32.4)
Southeastern Anatolia		8 (4.6)
Central Anatolia		23 (13.3)
Black Sea		10 (5.8)
Marmara		49 (28.3)
Location of practice	173	
State hospital		20 (11.6)
Training and research hospital		67 (38.7)
University		50 (28.9)
Private hospital		31 (17.9)
Private practice		5 (2.9)
Subspeciality	176	
General cardiology		74 (42.0)
Heart failure specialist		18 (10.2)
Cardiovascular imaging		9 (5.1)
Interventional cardiology		63 (35.8)
Electrophysiologist		12 (6.8)
Academic ranks	176	
Research assistant		10 (5.7)
Cardiologist		89 (50.6)
Cardiologist, Assistant professor		18 (10.2)
Cardiologist, Associate professor		36 (20.5)
Cardiologist, Professor		23 (13.1)

Values are given as mean ± standard deviation or n (%).

Ejection Fraction Cut-Off Value to Define HFrEF

For most cardiologists (80.1%), an ejection fraction of 40% was the accepted cut-off value to define HFrEF (Figure 1A). In the subgroup analysis, 85.6% of physicians aged ≤ 40 years accepted an ejection fraction of 40% as the cut-off value to define HFrEF compared to 70.8% among those aged > 40 years (*P* = 0.061). There were no significant differences between genders, geographic regions, locations of practice, or academic ranks.

ACEi or ARNi Choice in Patients with *De Novo* HFrEF: Which One is the First?

Approximately two-thirds of the study participants (n = 111, 62.7%) would initiate HF treatment with an ACEi instead of an ARNi in patients with *de novo* HFrEF (Figure 1B). A broad majority of cardiologists (91.3%) responded that the main reason for prescribing ACEi instead of ARNi is the reimbursement regulations of the Social Security Institution in Türkiye.

Although two-thirds of the study participants responded that they prescribe ACEi instead of ARNi in patients with *de novo* HFrEF, the majority of participants who practice in a university hospital with an academic rank would start medical therapy with an ARNi (university hospital 54.0% vs. state hospital 10.0%, *P* = 0.008) (Figure 1C-D). The present survey revealed that starting medical therapy with an ARNi instead of an ACEi in patients with *de novo* HFrEF was more common among HF specialists than non-specialists (72.2% vs. 33.3%, *P* = 0.001) (Figure 1B). There were no significant differences in other subgroup analyses, including age, gender, and geographic regions.

Up-titration of Current Medications or Adding Another Class of HF Medication: Which One is More Important?

More than half of the participants (*n* = 91, 52.3%) stated that adding another class of HF medication is more important than up-titrating those already started. This result was consistent across all subgroups.

Starting and Sequencing Approaches

In response to the question, "*What is your standard heart failure drug prescription strategy in a patient with a first episode of*

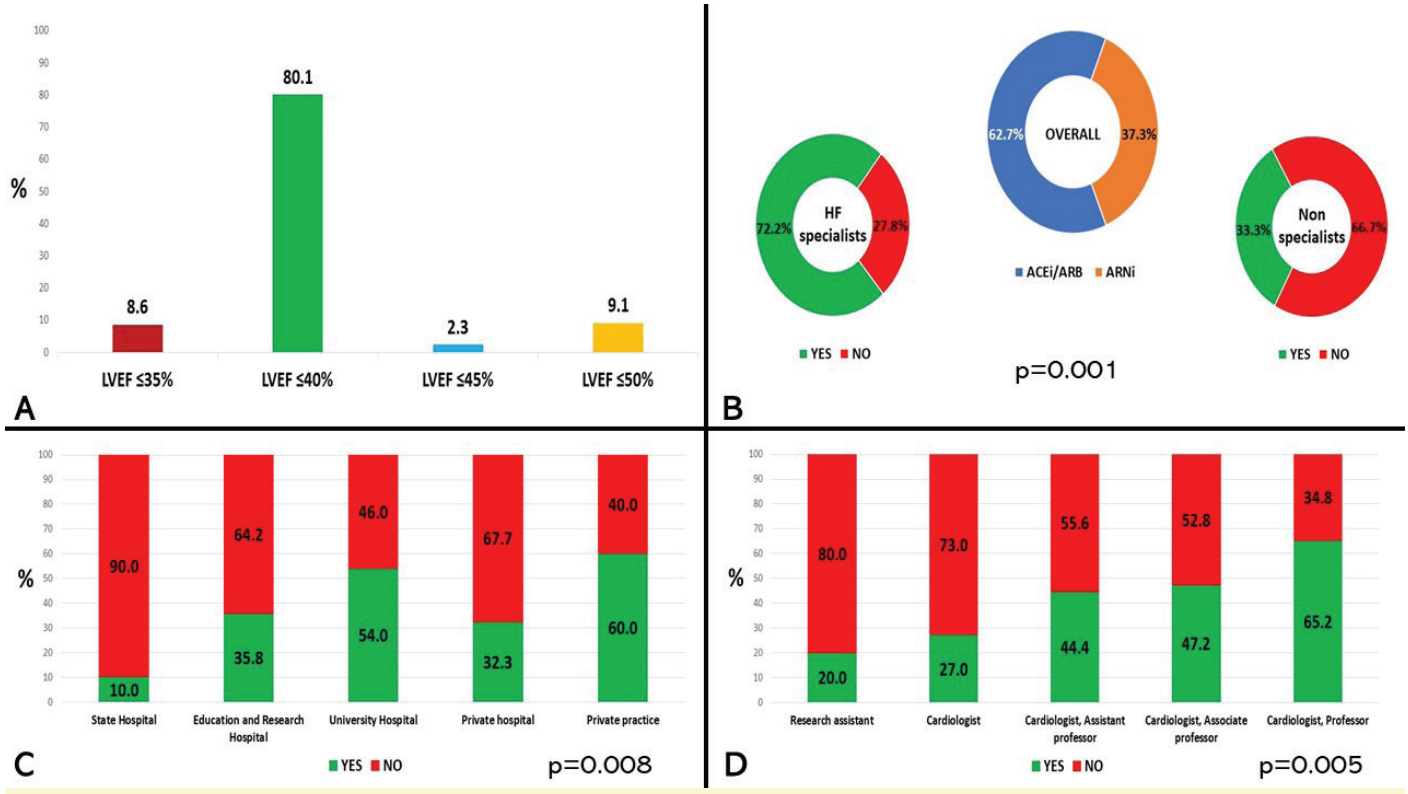

Figure 1. Accepted ejection fraction cut-off values for defining heart failure with reduced ejection fraction (HFrEF) among survey participants (A); responses to the question "*ACEi (angiotensin-converting enzyme inhibitor) or ARNi (angiotensin receptor-neprilysin inhibitor) choice in patients with de novo HFrEF: Which one is the first?*" (B); responses to the question "*Do you start HF treatment with an ARNi instead of an ACEi in patients with de novo HFrEF*" according to heart failure (HF) specialists versus non-specialists (B), location of practice (C), and academic rank (D).

HFrEF?", the majority of the participants preferred the historical approach, starting with ACEi or ARNi first (*n* = 116, 69.3%), followed by beta-blockers (*n* = 78, 46.1%), MRAs third (*n* = 97, 56.4%), and SGTL2i (*n* = 57, 33.1%) fourth.

Although the majority of cardiologists preferred the historical approach, more than two-thirds of the study participants (*n* = 123, 69.5%) also declared that it is possible to prescribe all four classes of HF medications during the index hospitalization period. A total of 58.5% of physicians aged over 40 years felt it was possible to start all four drug classes during the index hospitalization, compared to 75.7% among physicians aged 40 years or younger (*P* = 0.017). Similarly, more than 70% of cardiologists working in state or training and research hospitals would initiate all four HF medications during the hospitalization period, versus only 51.6% among physicians working in private hospitals (*P* = 0.018). There were no significant differences between sex, geographic regions, or academic ranks.

Up-Titration Period and Maximally Tolerated Doses of HF Medications

In clinical practice, the most realistic time to achieve the maximally tolerated doses for all four HF medications was three months for 42.1% (*n* = 74) of participants, followed by one month for 33.5% (*n* = 59), 15 days for 10.2% (*n* = 18), and six months for 10.2% (*n* = 18). There were no significant differences in the subgroup analysis except among physicians with academic ranks. Although more than 40% of participants with academic rank declared that the most realistic time to reach maximal up-titration was three months, 50% of research assistants believed that the maximal up-titration time was only one month (*P* = 0.028) (Figure 2A).

The majority of physicians (*n* = 92, 52.0%) reported that they could achieve maximally tolerated doses of HF medications in 26% to 50% of patients, followed by 23.7% (*n* = 42) in 51% to 75% of patients, and only 3.4% (*n* = 6) in 75% or more of patients. HF specialists were more dedicated to optimizing and up-titrating HF medications compared to non-specialists (*P* = 0.013) (Figure 2B).

Efficacy Perception of HF Medication Classes

In response to the question "*If you had to choose only one heart failure medication class for a patient with HFrEF, which medication class would you choose?*", 44.1% of cardiologists answered ARNi (n = 78), followed by beta-blockers in 23.7% (*n* = 42), ACEi at 22.0% (*n* = 39), SGLT2i at 7.3% (*n* = 13,) and finally MRAs at 2.8% (*n* = 5) (Figure 3A). In the subgroup analysis, 83.3% of the HF specialists answered ARNi versus only 39.6% among non-HF specialists (*P* = 0.009) (Figure 3B). There were no significant differences in other subgroup analyses.

ARNi treatment was considered the most efficient heart failure medication by 52.6% of physicians, followed by ACEi at 20.7%, beta-blockers at 18.2%, SGTL2i at 6.4%, and MRAs at 2.1%.

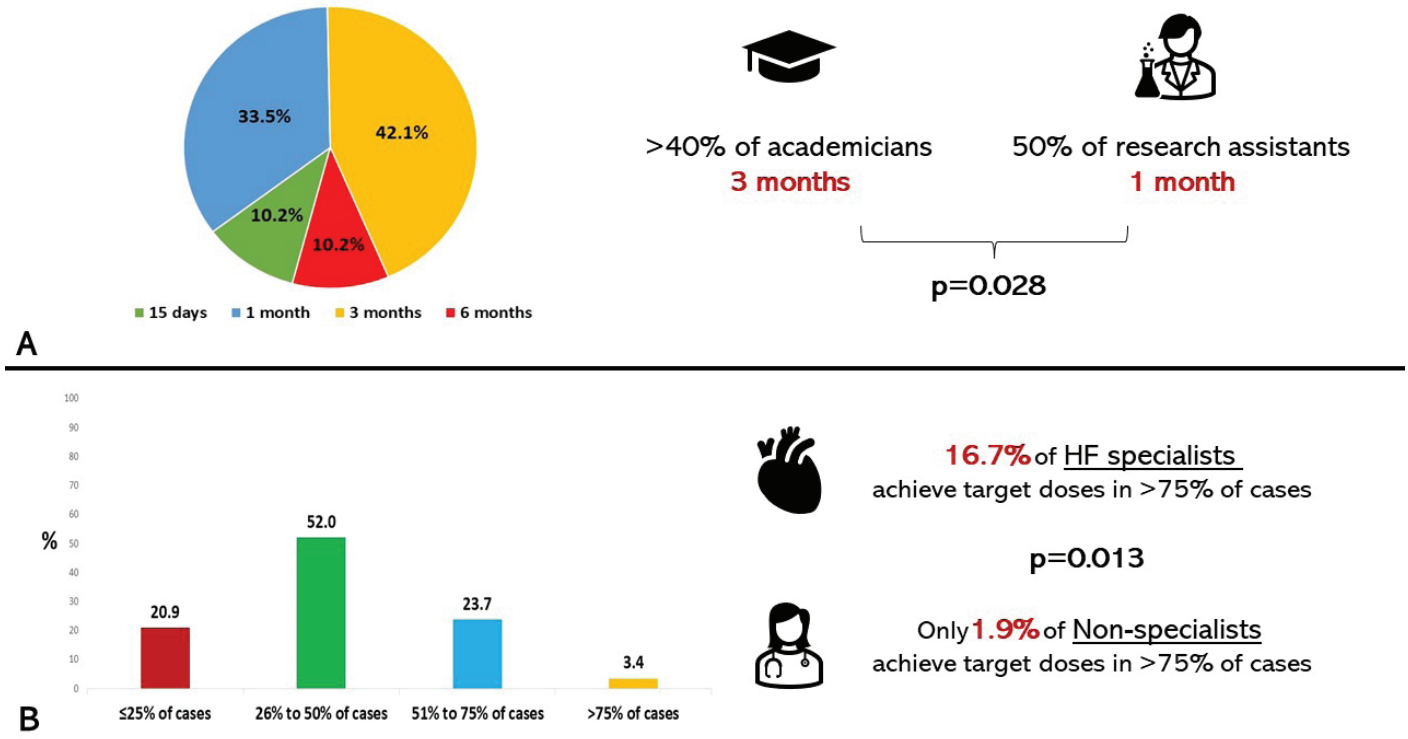

Figure 2. The most realistic time to reach maximal up-titration of HF medications and the differences between participants with an academic rank and research assistants (A); responses to the question "*How many patients do you achieve titration to full doses in clinical routine?*" and the differences between HF specialists versus non-specialists (B).

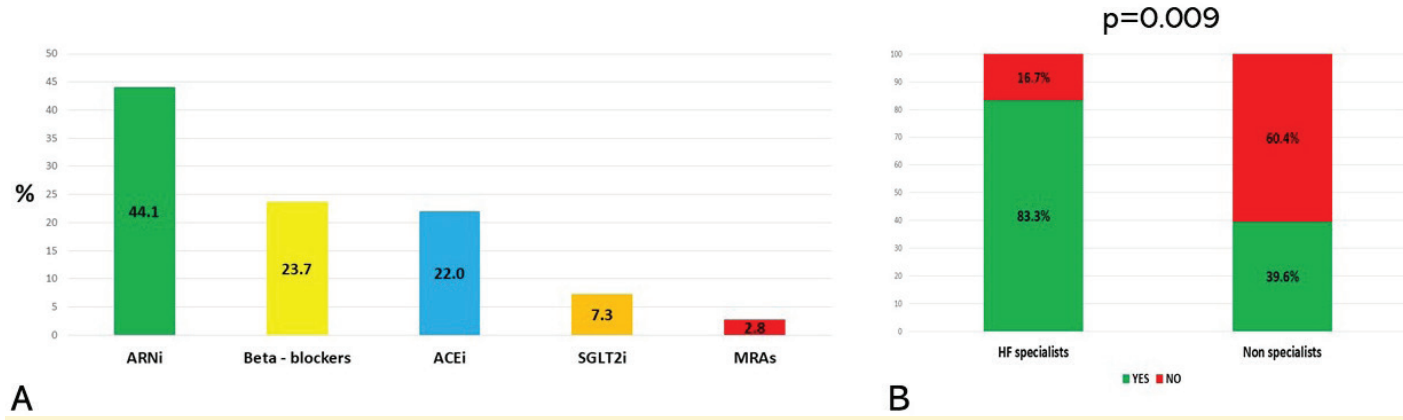

Figure 3. Responses to the question "*If you had to choose only one heart failure medication class for a patient with HFrEF, which medication class would you choose?*" (A); and 83.3% of HF specialists answered ARNi to the same question versus only 39.6% among non-HF specialists (B).

In response to the question, "*Low dose of each of the four classes of heart failure medications or three classes of heart failure medications at the maximal tolerated dose: which strategy is better?*", approximately two-thirds of the cardiologists (*n* = 107, 60.8%) answered that prescribing a low dose of the four classes of heart failure medications is better than three classes of at the maximal dose. There were no other statistical differences across the subgroup analyses.

Outpatient Visit Schedule After Hospital Discharge

Generally, 49.2% of physicians (*n* = 87) declared that the most appropriate time for the outpatient visit is one week after hospital discharge, followed by 15 days after discharge (37.9%) and one month after discharge (10.8%). There were no significant differences across the subgroup analyses.

Mineralocorticoid Receptor Antagonist Treatment in Patients with Glomerular Filtration Rate < 30 mL/min and/or Serum Potassium Level 5.0-5.5 µmol/L

Only one-fourth of cardiologists (*n* = 43, 24.3%) chose to start MRAs even if the glomerular filtration rate is less than 30 mL/min (Figure 4A). There were no significant differences across the subgroup analyses.

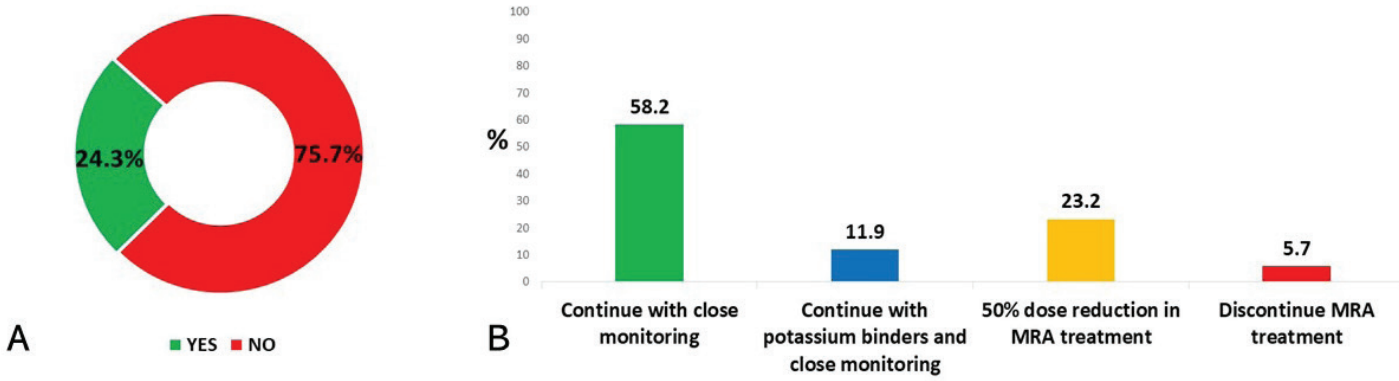

Figure 4. Introduction of mineralocorticoid receptor antagonists (MRAs) in HFrEF patients with a glomerular filtration rate (GFR) < 30 mL/min (A); and responses to the question "*What is your management strategy in patients with a serum potassium level of 5.0-5.5 µmol/L and receiving MRA treatment?*" (B).

Table 2. The Most Common Side-Effects of Heart Failure Medications

Angiotensin-Converting Enzyme Inhibitors	**n (%)**
Cough	126 (71.2)
Symptomatic hypotension	27 (15.3)
Worsening of renal function	20 (11.3)
Hyperkalemia	3 (1.7)
Angioedema	–
Angiotensin Receptor-Neprilysin Inhibitors	
Symptomatic hypotension	143 (81.7)
Worsening of renal function	19 (10.9)
Hyperkalemia	8 (4.6)
Cough	2 (1.1)
Angioedema	–
Beta Blockers	
Bradycardia	106 (59.9)
Erectile dysfunction	40 (22.6)
Symptomatic hypotension	16 (9.0)
Worsening of COPD	6 (3.4)
Worsening of heart failure	6 (3.4)
Mineralocorticoid Receptor Antagonists	
Hyperkalemia	134 (75.7)
Worsening of renal function	27 (15.3)
Gynecomastia	12 (6.8)
Symptomatic hypotension	4 (2.3)
Sodium-Glucose Co-Transporter 2 (SGLT-2) Inhibitors	
Urinary tract infection	83 (49.1)
Worsening of renal function	32 (18.9)
None	20 (12.0)
Symptomatic hypotension	19 (11.2)
Ketoacidosis	5 (3.0)
Other side-effects*	10 (6.0)

COPD, Chronic Obstructive Pulmonary Disease.
*Six participants declared, "*I have no experience with SGLT-2 inhibitors*," dysuria and polyuria without a urinary tract infection (2 participants), weight loss (1 participant), and symptomatic hypoglycemia.

In response to the question, "*What is your management strategy in patients with serum potassium levels 5.0-5.5 µmol/L and receiving MRA treatment?*", more than half of the participants (*n* = 103, 58.2%) stated that they continue MRA treatment with close serum potassium monitoring. A total of 41 physicians (23.2%) decided on a 50% dose reduction in MRA treatment, and 10 physicians (5.7%) decided to discontinue MRA treatment due to hyperkalemia (Figure 4B). There were no significant differences across the subgroup analyses.

Monitoring of Iron Status in Patients with HFrEF

In response to the question "*How often do you check the iron status in patients with HFrEF?*", most participants (*n* = 75, 42.6%) responded that they check the iron status every six months, followed by at each outpatient visit (15.3%), randomly (14.2%), and at each hospitalization period (10.8%). In contrast, 5.1% of physicians stated that they do not monitor iron status in patients with HFrEF. There were no significant differences across the subgroup analyses.

The Most Common Side Effects of Heart Failure Medications

According to the study participants, cough was the most common side effect of ACEi (*n* = 126, 71.2%), symptomatic hypotension with ARNi (*n* = 143, 81.7%), bradycardia with beta-blockers (*n* = 106, 59.9%), hyperkalemia with MRAs (*n* = 134, 75.7%), and urinary tract infections with SGLT2i (*n* = 83, 49.1%). The most common side effects of each heart failure medication class are presented in Table 2.

Discussion

The present survey provides detailed information about the opinions of cardiologists on HFrEF management in Türkiye. The principal findings of this survey are as follows: (i) an ejection fraction of 40% is the preferred cut-off value to define HFrEF for most cardiologists; (ii) although more than half of the participants considered ARNi treatment as the most efficient heart failure medication, about two-thirds of them stated that they initially initiate treatment with ACEi instead of ARNi due to reimbursement regulations and cost issues; (iii) starting another class of heart failure medication was perceived as more important than up-titration of those already started; (iv) although the majority of cardiologists declared that it is possible to start all four classes of heart failure medications before discharge, the

sequential historical approach remained the preferred strategy for HFrEF management.

Left ventricular ejection fraction is the cornerstone of heart failure classification and evidence-based treatment selection. However, various cut-off values for ejection fraction have been described to identify patients with HFrEF in previous clinical trials.[8-11] In the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial, an ejection fraction of 35% was the accepted cut-off value to define 'systolic' heart failure, whereas it was 45% in the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial.[8,9] The MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) enrolled HFrEF patients with an ejection fraction of 30% or less, and those with ≤ 40% in the DAPA-HF trial (Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure Trial).[10,11] Although the universal classification of heart failure defined HFrEF as an ejection fraction of 40% or less, the cut-off value for HFrEF is still controversial among cardiologists.[12] An international cardiology survey reported that the threshold to define HFrEF was ≤ 40% for only 61% of the physicians.[7] In our survey, the vast majority of cardiologists (80.1%) in Türkiye preferred the cut-off value of 40% for HfrEF, which is more compatible with current heart failure guidelines.[1,2]

The PARADIGM-HF (Prospective comparison of ARNi with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure) trial compared ARNi LCZ696 (sacubitril/valsartan) with enalapril in patients with HFrEF and showed that LCZ696 was superior to enalapril in reducing the risks of death and hospitalization for heart failure.[13] After two years, the 2016 European Society of Cardiology (ESC) heart failure guideline recommended ARNi treatment in HFrEF management with a class 1 recommendation for the first time.[14] Moreover, the recently published American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) heart failure guideline recommended the use of ARNi instead of ACEi in patients with HFrEF to reduce heart failure hospitalizations and/or death.[2] However, the implementation of heart failure guidelines' recommendations takes time in a real-life setting. For example, the ATA study (Adherence to guideline-directed medical and device Therapy in outpAtients with heart failure with reduced ejection fraction) reported that the rate of ARNi use was only 2.1% in patients with HFrEF.[4] In the present survey, ARNi treatment was considered the most efficient heart failure medication by cardiologists practicing in Türkiye. However, about two-thirds of the participants stated that they initiate heart failure treatment with an ACEi instead of ARNi in their daily clinical practice. The main reason for this situation was the reimbursement regulations in Türkiye. As mentioned in the introduction section, ARNi treatment is not included within the scope of reimbursement, thus the vast majority of eligible patients could not use it due to its cost, according to the physicians. It is clear that the reimbursement criterion of the Social Security Institution in Türkiye for ARNi treatment is not in accordance with current scientific evidence and guideline recommendations. We believe there is a need for organized action for the reimbursement of ARNi by healthcare providers, and the prescription of ARNi treatment should be left to the physician's discretion without any restriction.

Although previous heart failure guidelines recommend a sequential step-by-step approach for the management of HFrEF, current European and American guidelines suggest starting all four classes of medications simultaneously.[2,3,14] Recently published STRONG-HF trial (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testinG, of Heart Failure Therapies) and a network meta-analysis have shown a significant association between the simultaneous use of all four classes of HF medications and a reduction in re-hospitalization rates and death.[15,16] Greene et al.[17] have recommended the simultaneous initiation of quadruple therapy during the index hospitalization. Despite clear evidence-based data and recommendations from guidelines, our survey revealed that the traditional sequential step-by-step approach remains the preferred approach among cardiologists practicing in Türkiye. Interestingly, most cardiologists also answered that a simultaneous start of quadruple therapy within the initial hospitalization may be feasible. This discrepancy between clinical choices and theoretical knowledge among cardiologists in Türkiye could be related to several physician-related factors including fear of side effects, a focus on eliminating symptoms rather than reducing mortality, and lack of motivation.

Another critical point demonstrated by this survey is the paradigm shift toward prescribing low doses of all four classes of HF medications instead of titrating any single HF medication class to the target dose. Data from the Swedish HF registry showed that using two HF medications at a moderated dose is associated with a lower risk of hospitalization and cardiovascular death compared to using any one-class medication at a maximal dose.[18] A multinational study comprising 6,787 patients with HFrEF reported that achieving more than 50% of the guideline-recommended target doses of ACEi and ß-blockers is associated with a lower risk of all-cause mortality than achieving the target dose of any one-class medication.[19] Consistent with current evidence, our survey demonstrated that approximately two-thirds of cardiologists practicing in Türkiye declared that prescribing low doses of quadruple therapy is more beneficial than using any three classes of medications at the target dose.

The PIONEER-HF trial (the comParIson Of sacubitril/valsartaN versus Enalapril on Effect on nt-pRo-bnp in patients stabilized from an acute Heart Failure episode) showed that the initiation of ARNI treatment is associated with a greater reduction in the N-terminal pro b-type natriuretic peptide (NT-proBNP) level than enalapril in patients with acute decompensated heart failure.[20] Furthermore, the initiation of sacubitril/valsartan during the index hospitalization or shortly after discharge in patients with acute heart failure was feasible in the TRANSITION trial (pre-discharge and posT-discharge tReatment initiation with sacubitril/valsartan inheArt failure patieNtS with reduced ejectIon-fracTionhospItalised for an acute decOmpensation eveNt).[21] About one-third of the study population in both trials were *de novo* HF patients.[20,21] In light of this evidence, the 2022 AHA/ACC/HFSA HF guideline stated that sacubitril/valsartan should be started in *de novo* HF patients with acute HFrEF before discharge.[2] In the present survey, in response to the question, "*sacubitril/valsartan or ACEi choice in patients with de novo HFrEF: Which one is the first?*", 72.2% of HF specialists answered ARNi instead of ACEi. However, this rate was only 33% among non-HF specialists. Being a heart failure specialist appears to

be associated with evidence-based heart failure treatment approaches.

Another significant difference in the subgroup analysis was about the up-titration period of HF medications. Although the majority of senior cardiologists stated that the most realistic time to achieve the target doses of HF medications was three months, this time period was only one month for research assistants. The STRONG-HF trial demonstrated a significant association between rapid up-titration of Guideline-Directed Medical Therapy (GDMT) and a reduced risk of 180-day all-cause death or heart failure readmission.[15] Based on the results of the STRONG-HF trial, the 2023 update of the European guideline recommended rapid up-titration of HF medications to reduce HF readmission or all-cause death.[3] Interestingly, the management approach of research assistants in Türkiye appears to be more compatible with current evidence than that of senior cardiologists. This may be attributed to research assistants being educated in an academic environment and adhering more closely to current guidelines and publications.

This study had some limitations. First, the main limitation of the present survey is its small sample size. Second, although this survey collected data from cardiologists practicing in seven geographical regions of Türkiye, some geographic areas may have been underrepresented. Third, the participants were relatively young, which may not reflect the profile of cardiologists aged over 40 years old. Fourth, participating in this survey may be correlated with a heightened interest in heart failure among cardiologists, thus, the results of the survey may be overestimated due to response bias. In this regard, the obtained data may not be representative of all cardiologists in Türkiye.

Conclusion

The present survey demonstrated significant gaps between guideline recommendations and the real-life clinical practice of cardiologists in Türkiye. Although ARNi treatment was considered the most efficient HF medication by physicians, the majority of them would initiate treatment with an ACEi due to reimbursement regulations and cost issues. In addition to ARNi treatment, SGLT2i treatment is also not included within the scope of reimbursement by the Social Security Institution in patients with HF without diabetes. Therefore, these novel HF treatments cannot be prescribed extensively for patients with HF. These results suggest that there is a need for organized action and close collaboration between the Ministry of Health, the Social Security Institution, and the Turkish Society of Cardiology to improve the implementation of guideline recommendations.

Ethics Committee Approval: This study was approved by the Başkent University Medical and Health Sciences Ethics Committee (Project No. KA19/58, Approval Number: 94603339-604.01.02/-7720, Date: 25.02.2019).

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Supplementary Table. Survey Questions

Number	Question	Response
1	Age	[Free text]
2	Gender	Female / Male
3	In which geographical region are you working?	Mediterranean Eastern Anatolia Aegean Southeast Anatolia Central Anatolia Black Sea Marmara
4	Which type of hospital do you work in?	State Hospital Training and Research Hospital University Hospital Private Hospital Private Practice
5	Which field of cardiology are you working in?	General/Clinical Cardiology Heart Failure Interventional Cardiology Cardiac Imaging Electrophysiology/Arrythmia Intensive Care Research Assistant/Cardiology Assistant
6	In your daily clinical practice, which ejection fraction cutoff value do you prefer for the definition of "heart failure with low ejection fraction" (e.g. <35% or <40%)?	[Free text]
7	Rank/classify the following heart failure treatments from the one you think is **the most effective** [1] to the one you think is **the least effective** [5]	ACE inhibitor/ARB ARNI Beta-blockers MRA SGLT2 inhibitors No opinion
8	Do you think it is better to start each of the four heart failure drug classes **[ACEi/ARB/ARNI, beta-blocker, MRA, SGLT2 inhibitor]** at a low dose than to use the 3 heart failure drug classes at the maximal tolerated dose?	Yes / No
9	In which order would you start/prefer the following heart failure in a newly diagnosed HFrEF patient? (1: I start first / 4: I prefer last)	ACE inhibitor/ARB ARNI Beta-blockers MRA SGLT2 inhibitors
10	In your daily practice, do you start ARNI instead of ACEi/ARB therapy in your first-diagnosis HFrEF patient who has not received any previous heart failure therapy? (Please answer according to your daily practice, not according to the guidelines)	Yes / No
11	In a patient with HFrEF who you hospitalized with a diagnosis of heart failure, do you initiate all 4 heart failure treatment classes during hospitalization/prior to discharge? (Please answer according to your daily practice, not according to the guidelines)	Yes / No
12	In your daily clinical practice, what do you think is the time required to reach the "target/maximal tolerated dose" of each of the four classes of heart failure drugs?	1 week 15 days 1 month 6 months 12 months
13	Do you think it is more important to up-titrate the dose of heart failure medications a patient is currently taking than to add a new class of heart failure medication?	Yes / No
14	Do you start MRA therapy (spironolactone or eplerenone) in your heart failure patients with GFR <30 mL/min?	Yes / No

Supplementary Table. Survey Questıons (*continued*)

Number	Question	Response
15	How often do you assess the iron status (ferritin + transferrin saturation) of your heart failure patients?	Every hospitalization At every outpatient checkup Every 6 months 1 time per year Random
16	In your daily clinical practice, what is the most important side effect you expect during ACE inhibitor therapy?	Symptomatic hypotension Worsening of kidney function Hyperkalemia Cough Angioedema
17	In your daily clinical practice, what is the most important side effect you would expect during ARNI treatment?	Symptomatic hypotension Worsening of kidney function Hyperkalemia Cough Angioedema
18	In your daily clinical practice, what is the most important side effect you expect during MRA treatment?	Symptomatic hypotension Worsening of kidney function Hyperkalemia Gynecomastia Other hormonal side effects
19	In your daily clinical practice, what is the most important side effect you expect during beta-blocker therapy?	Symptomatic hypotension Bradycardia Worsening heart failure Bronchoconstriction/COPD worsening Erectile dysfunction
20	In your daily clinical practice, what is the most important side effect you would expect during SGLT2 inhibitor treatment?	Symptomatic hypotension Worsening of kidney function Ketoacidosis Urinary tract infection
21	In your daily clinical practice, in what percentage of your heart failure patients do you reach the target treatment dose?	<%25 %26-50 %51-75 >%75
22	If you had to choose only 1 drug for the treatment of heart failure, which drug would you choose?	ACEi/ARB ARNI Beta-blockers MRA SGLT2 inhibitors