

Adherence to guideline-directed medical and device Therapy in outpatients with heart failure with reduced ejection fraction: The ATA study

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ABSTRACT

Objective: Despite recommendations from heart failure guidelines on the use of pharmacologic and device therapy in patients with heart failure with reduced ejection fraction (HFrEF), important inconsistencies in guideline adherence persist in practice. The aim of this study was to assess adherence to guideline-directed medical and device therapy for the treatment of patients with chronic HFrEF (left ventricular ejection fraction $\leq 40\%$).

Methods: The Adherence to guideline-directed medical and device Therapy in outpatients with HFrEF (ATA) study is a prospective, multicenter, observational study conducted in 24 centers from January 2019 to June 2019.

Results: The study included 1462 outpatients (male: 70.1%, mean age: 67 ± 11 years, mean LVEF: $30\% \pm 6\%$) with chronic HFrEF. Renin-angiotensin system (RAS) inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and ivabradin were used in 78.2%, 90.2%, 55.4%, and 12.1% of patients, respectively. The proportion of patients receiving target doses of medical treatments was 24.6% for RAS inhibitors, 9.9% for beta-blockers, and 10.5% for MRAs. Among patients who met the criteria for implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT), only 16.9% of patients received an ICD (167 of 983) and 34% (95 of 279) of patients underwent CRT (95 of 279).

Conclusion: The ATA study shows that most HFrEF outpatients receive RAS inhibitors and beta-blockers but not MRAs or ivabradin when the medical reasons for nonuse, such as drug intolerance or contraindications, are taken into account. In addition, most eligible patients with HFrEF do not receive target doses of pharmacological treatments or guideline-recommended device therapy. (*Anatol J Cardiol 2020; 24: 32-40*)

Keywords: adherence, chronic heart failure, device therapy, guidelines, pharmacological treatment, outpatients

Introduction

Chronic heart failure (HF) is a major public health problem that results in a significant burden on the health system (1). Chronic HF affects approximately 265 million people in the developed world and 475 million people in developing countries (2). The current prevalence of HF in Turkey is about 1.5 million patients, which is estimated to increase to 3 million people in the near future (3). Although treatment options for chronic HF have improved in past years with the development of new drugs and device therapies, HF remains associated with high mortality and rehospitalization rates (4).

The use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), ivabradine, and, more recently, angiotensin receptor-neprilysin inhibitor (ARNI) has been associated with improved clinical outcomes and survival in patients with heart failure with reduced ejection fraction (HFrEF). HF guidelines recommend the use of these drugs at maximally tolerated target doses to reduce mortality and/or rehospitalizations due to HF (4, 5). However, implementing guideline recommendations into clinical practice takes time. For example, the proportion of HF patients treated with beta-blockers in European countries has increased from 37% to 91% over 15 years (6). On the other hand, the proportion of HF outpatients treated with maximally targeted doses is very far from the current guideline recommendations. Only 30% of HF patients are treated with the target maximally tolerated dosage of these drugs (7). Similarly, observational studies and registry data suggest that only a one-third of eligible chronic HF patients receive implantable cardioverter-defibrillator (ICD) therapy, and one-fifth of eligible chronic HF patients receive cardiac resynchronization therapy (CRT) (8, 9). Although adherence to the treatment recommendations of HF guidelines is associated with improved survival, it is usually suboptimal in clinical practice because of physician and/or patient-related reasons that are unclear (10, 11).

The Adherence to guideline-directed medical and device Therapy in outpatients with heart failure with reduced ejection

fraction (ATA) study aims to determine (1) the percentage of HF patients who received the treatments recommended in the current HF guidelines, (2) the frequency of physician or patient-related reasons and medical contraindications among patients with HFrEF who do not receive guideline-directed therapies, (3) the proportion of HF patients receiving treatment at target doses as recommended in the guidelines, and (4) the reasons for non-prescription of medical therapies at the target doses.

Methods

The ATA study is a prospective, multicenter, observational study of HF outpatients including 24 cardiology centers in seven geographical regions in Turkey. Outpatients with chronic HF with reduced ejection fraction (left ventricular ejection fraction $\leq 40\%$) from 4 university hospitals, 10 education and research hospitals, 7 state hospitals, and 3 private hospital outpatient clinics were included between January 2019 and June 2019 (Fig. 1).

Outpatients with chronic HF with reduced ejection fraction were included in the ATA study if the diagnosis of HF was based on the criteria of current HF guidelines (i.e., symptoms and signs related to HF and left ventricular ejection fraction $\leq 40\%$) (4, 5). Patients with acute decompensated HF, de novo HF, chronic HF with preserved ejection fraction (left ventricular ejection fraction $> 40\%$), and age less than 18 years were excluded from the ATA study. Patient data including demographic features, cardiovascular symptoms and risk factors, medical history, physical examination findings, electrocardiographic and echocardiographic data, laboratory results, and current medical treatments were collected on the first visit. Baseline echocardiographic data, including assessment of left ventricular ejection fraction, were obtained for the entire study population on the first visit.

The study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients gave written informed consent to participate. This study was approved by Başkent University Institutional Review Board and Ethics Committee (Project No. KA19/58).

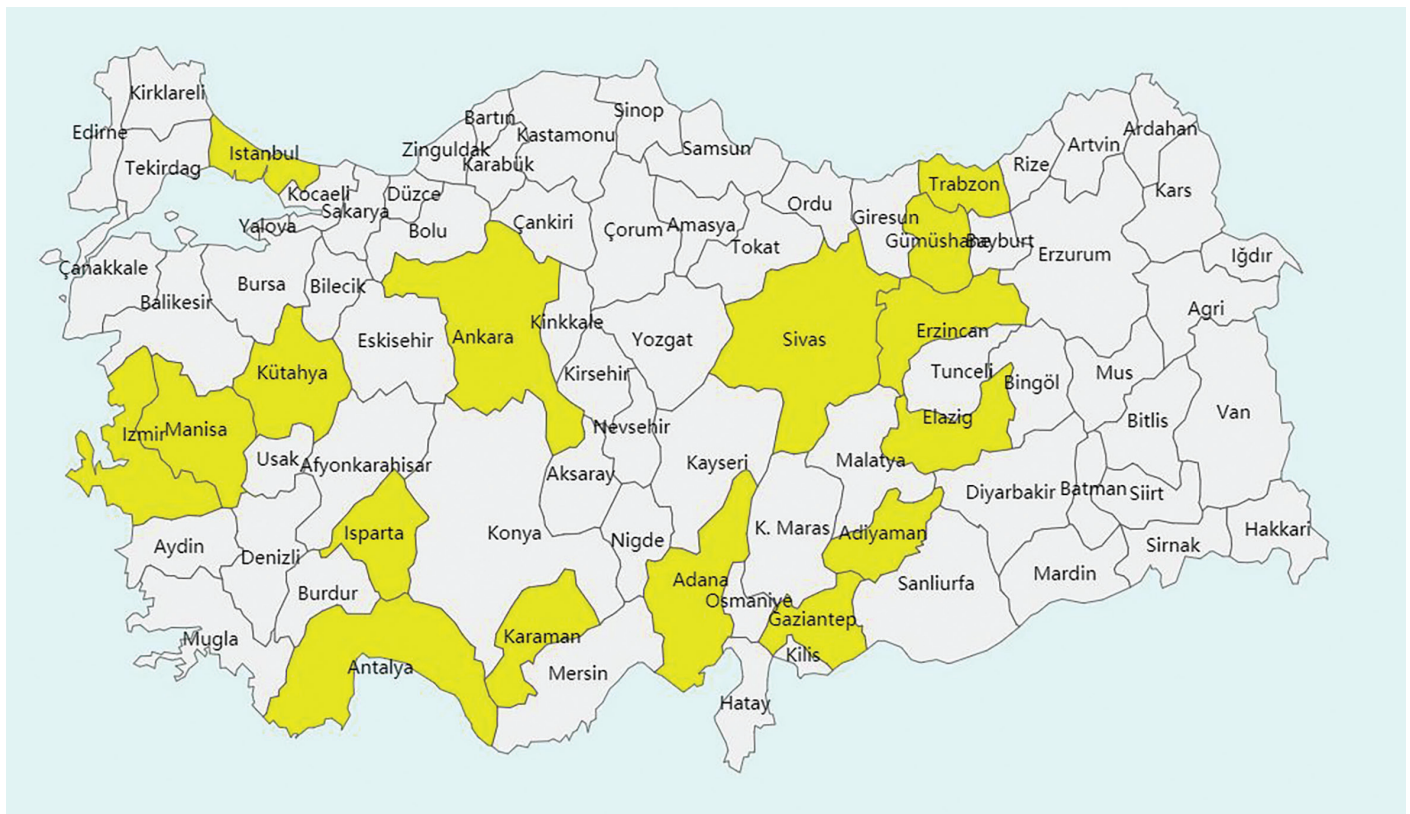


Figure 1. Cities of participating investigators and centers

Statistical analysis

The continuous variables are reported as mean \pm standard deviation or median and interquartile range, and the categorical variables are expressed as frequencies and percentages. SPSS software (SPSS, Inc., Chicago, IL, USA) for Windows, version 22.0, was used for statistical analyses.

Results

The study included 1462 outpatients with HF_{rEF}. Baseline characteristics of the study population are presented in Table 1. The mean age of the patients was 67 ± 11 years, and there was a predominance of male patients (1025 men, 70.1%). The etiology of HF was ischemic in 67.9% of patients, and 52.5% had a history of acute myocardial infarction. Most of the study population were New York Heart Association class I or II (22.4% and 53.4%, respectively), and the mean left ventricular ejection fraction on echocardiographic examination was $30\% \pm 6\%$. The mean duration of HF was 2.4 ± 2.6 years before study initiation, and 43.6% of patients had a history of hospitalization due to acute decompensated HF.

The most frequent comorbidities were hypertension (57.8%), dyslipidemia (38%), diabetes mellitus (34.7%), atrial fibrillation (23.7%), chronic lung disease (23.2%), chronic kidney disease (18.1%), anemia (17.4%), thyroid disease (9.5%), depression (6.9%), peripheral artery disease (6%), stroke (5.7%), and malignancy (4.6%).

The patients' mean systolic blood pressure was 121 ± 17 mm Hg, and 24.5% had a systolic blood pressure < 110 mm Hg. The mean heart rate was 78 ± 16 bpm; 72.8% of the cases were in sinus rhythm, and 65% of the study population had a heart rate ≥ 70 bpm. Left bundle branch block (LBBB) and non-LBBB (i.e., right bundle branch block or nonspecific ventricular conduction delay) were detected by electrocardiography in 15.9% and 11.9% of cases, respectively.

Renin-angiotensin system (RAS) inhibitors (ACEi or ARBs, or ARNI), beta-blockers, MRAs, and ivabradin were prescribed in 78.2%, 90.2%, 55.4%, and 12.1% of the patients before study enrollment, respectively. Baseline pharmacological treatments are shown in Table 2. The most common reasons for nonuse of RAS inhibitors were severe renal dysfunction, symptomatic hypotension, and hyperkalemia (Fig. 2). The main reasons for nonprescription of beta-blockers were bradyarrhythmia or target heart rate already achieved, symptomatic hypotension, and worsening of chronic obstructive pulmonary disease (Fig. 3). The most common reasons for nonuse of MRAs were severe renal dysfunction, hyperkalemia, and left ventricular ejection fraction of 36%–40% (Fig. 4). When we excluded all of these medical reasons (drug intolerance or contraindication for nonuse of drugs), the real rate of undertreatment was determined to be 10.9%, 5.1%, and 28.8% for RAS inhibitors, beta-blockers, and MRAs, respectively (Fig. 2–4).

The proportions of HF patients receiving target doses of guideline-directed medications were 24.6% for RAS inhibitors, 9.9% for beta-blockers, and 10.5% for MRAs. The most com-

Table 1. Baseline characteristics of the study population

Variable	Study population: 1462 patients
Age (years)	67±11
Male	1025 (70.1)
Vital signs	
• Systolic blood pressure (mm Hg)	121±17
• Systolic blood pressure ≤110 mm Hg	358 (24.5)
• Heart rate (bpm)	78±16
• Heart rate ≥70 bpm	950 (65)
Functional class, NYHA I–II	1107 (75.8)
HF duration (years)	2.4±2.6
Prior HF hospitalization	637 (43.6)
Ischemic etiology	993 (67.9)
Comorbidities and risk factors	
• Coronary artery disease	1066 (72.9)
• Myocardial infarction	767 (52.5)
• Percutaneous coronary intervention	718 (49.1)
• Coronary artery bypass graft	295 (20.2)
• Hypertension	845 (57.8)
• Diabetes mellitus	507 (34.7)
• Dyslipidemia	556 (38)
• Atrial fibrillation	347 (23.7)
• Stroke or TIA	83 (5.7)
• Peripheral arterial disease	87 (6)
• Chronic kidney disease	265 (18.1)
• Asthma or COPD	339 (23.2)
• Anemia	254 (17.4)
• Thyroid disease	139 (9.5)
• Depression	101 (6.9)
• Cancer	67 (4.6)
• Current smoker	333 (22.8)
• Former smoker	538 (36.8)
Electrocardiographic data	
• Sinus rhythm	1064 (72.8)
• Atrial fibrillation	323 (22.1)
• Left bundle branch block	233 (15.9)
• QRS duration (ms)	108 ± 25
Echocardiographic data	
• Left ventricular ejection fraction (%)	30 ± 6
• Left atrial dilatation	1089 (74.5)
• Moderate-to-severe valve disease	755 (51.6)
• Systolic pulmonary artery pressure (mm Hg)	39±14
Laboratory data	
• Serum creatinine (mg/dL)	1.18±0.6

Table 1. Cont.

Variable	Study population: 1462 patients
• Glomerular filtration rate (mL/min/1.73 m ²)	68±22
• Hemoglobin (g/L)	13.1±1.8
• NT-proBNP (pg/mL)	3277±5264
• Thyroid stimulating hormone (mU/L)	1.9±1.8
• LDL-cholesterol (mg/dL)	103±33

Data are given as mean ± SD and n (%).
NYHA - New York Heart Association; HF - heart failure; TIA - transient ischemic attack;
COPD - chronic obstructive pulmonary disease; NT-proBNP - N-terminal pro-B-type natriuretic peptide; LDL - low-density lipoprotein

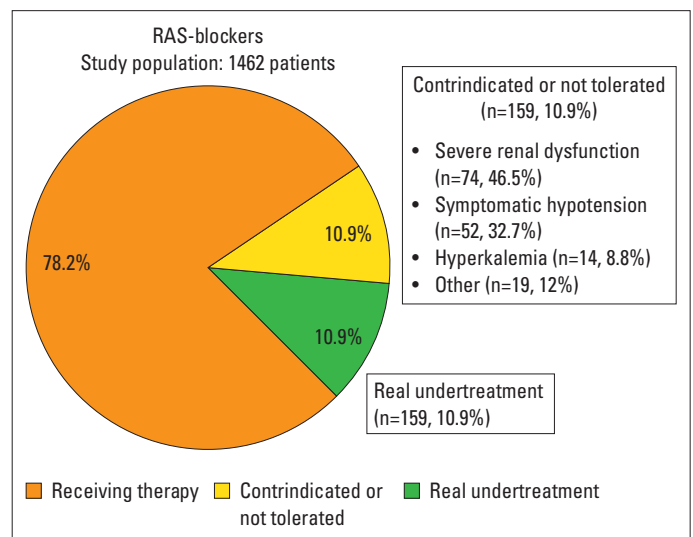


Figure 2. Reasons for nonuse of RAS blockers (ACEi, ARBs, and ARNI) in patients with HFrEF

RAS - renin angiotensin system; ACEi - angiotensin-converting enzyme inhibitors; ARBs - angiotensin receptor blockers; ARNI - angiotensin receptor–neprilysin inhibitor; HFrEF - heart failure with reduced ejection fraction

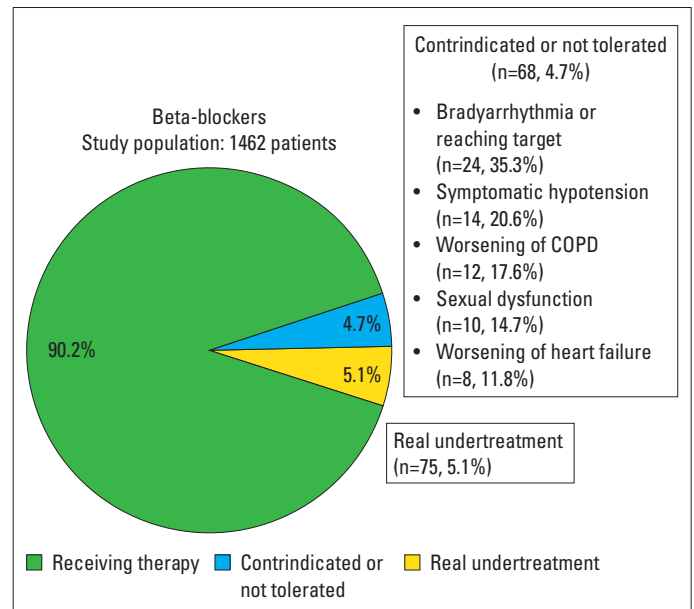
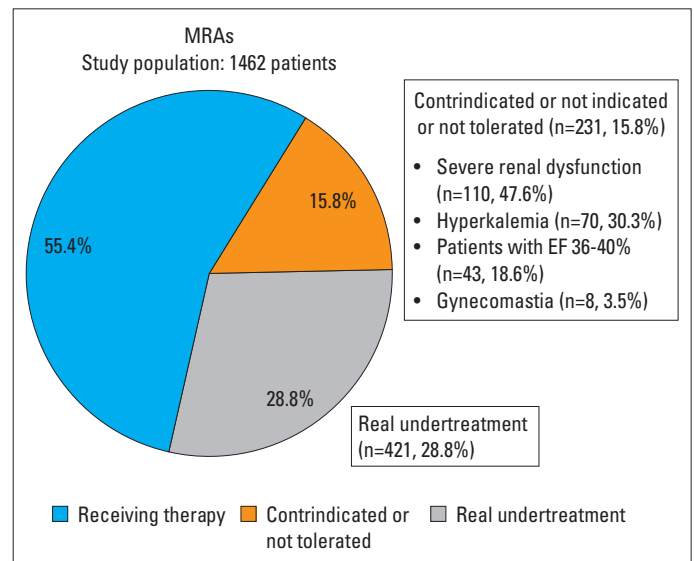
mon reasons for not using the target doses of RAS inhibitors were symptomatic hypotension, currently in the up-titration period, and worsening of renal function. Reasons for not using the target doses of beta-blockers were bradyarrhythmia or target heart rate already achieved, currently in the up-titration period, and symptomatic hypotension. The main reasons for nonprescription of target doses of MRAs were currently in the up-titration period, hyperkalemia, and worsening renal function. The real rate of under up-titration (absence of clear medical reasons for under up-titration) was determined to be 46.8%, 48.3%, and 59.8%, respectively, for RAS inhibitors, beta-blockers, and MRAs (Table 3).

Although more than two-thirds of the study population had sinus rhythm with a heart rate ≥70 bpm, the rate of ivabradine use was only 12.1%. Approximately two-thirds of patients were receiving diuretics (67.9%) and antiplatelet agents (67%). Statins and digoxin were prescribed to 45.6% and 12.2% of the patients, respectively (Table 2).

Table 2. Drug treatments in outpatients with HFrEF

Drug	Study population: 1462 patients
RAS inhibitors (ACEi+ARBs+ARNI)	1144 (78.2)
ACEi	869 (59.4)
• Ramipril	486 (33.2)
• Perindopril	230 (15.7)
• Zofenopril	61 (4.2)
• Trandolapril	34 (2.3)
• Lisinopril	20 (1.4)
• Fosinopril	15 (1)
• Enalapril	9 (0.6)
• Kaptopril	8 (0.5)
• Silazapril	6 (0.4)
ARBs	244 (16.7)
• Candesartan	96 (6.6)
• Valsartan	88 (6)
• Irbesartan	24 (1.6)
• Losartan	17 (1.2)
• Olmesartan	11 (0.8)
• Telmisartan	8 (0.5)
ARNI (sacubitril valsartan)	31 (2.1)
Beta-blockers	1319 (90.2)
• Metoprolol	641 (43.8)
• Carvedilol	475 (32.5)
• Bisoprolol	122 (8.3)
• Nebivolol	81 (5.5)
MRAs	810 (55.4)
• Spironolactone	762 (52.1)
• Eplerenone	48 (3.3)
Ivabradine	177 (12.1)
Diuretics	992 (67.9)
Digoxin	178 (12.2)
Statins	667 (45.6)
Antiplatelet agents	980 (67)
Warfarin	160 (10.9)
DOACs	225 (15.4)
Amiodarone	90 (6.2)
CCBs (dihydropyridine)	193 (13.2)
Nitrate	163 (11.1)
Trimetazidine	206 (14.1)
Ranolazine	93 (6.4)

Data are given as n (%).
RAS - renin-angiotensin system; ACEi - angiotensin-converting enzyme inhibitors;
ARBs - angiotensin receptor blockers; ARNI - angiotensin receptor-neprilysin inhibitor;
MRAs - mineralocorticoid receptor antagonists; DOACs - direct oral anticoagulants;
CCBs - calcium channel blockers

**Figure 3.** Reasons for nonuse of beta-blockers in patients with HFrEF
COPD - chronic obstructive pulmonary disease; HFrEF - heart failure with reduced ejection fraction**Figure 4.** Reasons for nonuse of MRAs in patients with HFrEF
MRAs - mineralocorticoid receptor antagonists; HFrEF - heart failure with reduced ejection fraction

Although ICD therapy was indicated in 67.8% of the study population, only 17.9% of patients underwent ICD therapy (11.4% ICD therapy and 6.5% CRT-D). Of the remaining cases, 40.3% of patients declared that the ICD therapy option was not offered to them by their physicians. In total, 80.9% of study population did not fulfill the criteria of the current HF guidelines for CRT. Among the patients who met the criteria for CRT, only 6.5% already had device implantation. In patients who met the current HF guideline criteria for ICD or CRT but who were not considered for device therapy (49.3% for ICD therapy and 12.6% for CRT), the main reason was that the physicians did not

Table 3. Heart failure patients at target dosages of recommended pharmacological treatments and reasons for not achieving target dosages

Study population: 1462 patients	Achieved	Achieved	Did not achieve	Reason for not achieving target dose	
	target dose	≥50%–<100% of target dose	target dose (<50% of target dose)		
RAS inhibitors (1144 patients, 78.3%)	282 (24.6)	478 (41.9)	384 (33.5)	Symptomatic hypotension	196 (22.7)
				Still in up-titration	171 (19.8)
				Worsening renal function	67 (7.8)
				Hyperkalemia	16 (1.9)
				Others	9 (1)
				No clear medical reason	403 (46.8)
Beta-blockers (1319 patients, 90.2%)	130 (9.9)	412 (31.2)	777 (58.9)	Bradyarrhythmia or reaching target heart rate	232 (19.5)
				Still in up-titration	229 (19.3)
				Symptomatic hypotension	96 (8.1)
				Worsening of COPD	32 (2.7)
				Worsening of heart failure	16 (1.3)
				Sexual dysfunction	7 (0.6)
				Others	3 (0.2)
				No clear medical reason	574 (48.3)
MRAs (810 patients, 55.4%)	85 (10.5)	710 (87.6)	15 (1.9)	Still in up-titration	144 (19.9)
				Hyperkalemia	72 (9.9)
				Renal dysfunction	52 (7.2)
				Gynecomastia	7 (0.9)
				Others	17 (2.3)
				No clear medical reason	433 (59.8)

Data are given as n (%). RAS - renin-angiotensin system; COPD - chronic obstructive pulmonary disease

Table 4. Device therapies

Implantable cardioverter-defibrillator	
• Implanted for primary prevention	133 (9.1)
• Implanted for secondary prevention	34 (2.3)
• Indicated but not recommended to the patient	590 (40.3)
• Patient refusal	131 (9)
• Not indicated	479 (32.8)
Cardiac resynchronization therapy	
• Implanted	95 (6.5)
• Indicated but not recommended to the patient	155 (10.6)
• Patient refusal	29 (2)
• Not indicated	1183 (80.9)

Data are given as n (%)

Discussion

Results of the ATA study reflect the real-life data on the pharmacological and nonpharmacological treatment options for patients with chronic HFrEF. In our study, we obtained detailed data on the phenotypic traits of patients with HF and rates of guideline-based medical therapy use; detailed dosage information on medical treatments, rates of use of the target dose, and reasons for not using drug and device therapies or not using these at target doses in patients with HF were also obtained.

The baseline characteristics, comorbidities, and clinical profiles other than the etiology of HF of the patient population included in the ATA study are similar to those of populations included in observational studies conducted in Europe and Turkey (1, 6, 7, 10, 12–14). Although the incidence of ischemic causes varied between 40% and 55% in studies conducted in Europe, this rate was found to be 67.9% in our study (1, 6, 7, 10). A higher incidence of ischemic causes in the ATA study compared with other studies indicates the need for a more rapid

evaluate the patients in terms of device therapy and/or did not offer the option of device therapy to the patients (40.3% for ICD therapy and 10.6% for CRT; Table 4).

and organized action in the diagnosis and pharmacoinvasive treatment of acute coronary syndromes, particularly ST-elevation myocardial infarction, and the need in our country to promote cardiac rehabilitation programs after acute myocardial infarction.

In our study, the rate of RAS inhibitor use was found to be lower than that in the registry studies conducted in Europe. RAS inhibitors were used in 88% of patients in the ESC-HF Pilot study and 92% of patients in the ESC Heart Failure Long-Term Registry. Although this rate is approximately 83% in the United States, it reaches up to 93% in Spain (12, 15). In the ATA study, contraindications or drug intolerance was reported in half of the patients who did not use a RAS inhibitor. Considering these reasons, the actual rate of inadequate treatment for RAS inhibitors is approximately 10%, which is acceptable. In the PARADIGM-HF study, the use of ARNI significantly decreased mortality compared with enalapril (16). Although ARNI has been recommended for use in patients with HFrEF with class I indication following PARADIGM-HF, the rate of ARNI use is only 2.1% in our study (4). The most probable reason for the low rate of ARNI use in our study might be the cost. ARNI is not included within the scope of reimbursement by the Social Security Institution in Turkey; thus, it cannot be prescribed extensively for patients with HFrEF. It seems reasonable to include ARNI treatment in the scope of reimbursement to achieve a higher rate of ARNI use in patients with HFrEF.

The rate of beta-blocker use in patients with HFrEF in the ATA study was found to be high. Nine of 10 patients with HFrEF receive beta-blocker therapy, and this rate is similar to that reported in the European and American registries (1, 7, 12, 15). Although the rates of RAS inhibitor and beta-blocker therapy use were satisfactory, the rate of MRA use was found to be low. In the ESC-HF Pilot study, the rate of MRA use in patients with HFrEF was 43% and increased up to 67% and 69% according to data from the ESC Heart Failure Long-Term Registry and QUALIFY study published in 2013 and 2016, respectively (1, 6, 7). According to the American registry data, the rate of baseline MRA use in patients with HFrEF was 35%, but this rate increased to 62% at the end of a 2-year follow-up (15). The results of the ATA study revealed that 1 of 2 patients with HFrEF were not receiving MRA treatment. Causes such as kidney failure, hyperkalemia, or gynecomastia were reported in one-third of patients not receiving MRAs treatment. When these patients were excluded, the actual rate of inadequate treatment of MRA was found to be approximately 30%, which is quite high. Physician awareness of MRA use should be increased, and physicians should be encouraged to use MRAs in patients with HFrEF in our country.

Another important observation revealed by this study is that compliance with guideline-based treatment recommendations for patients with HFrEF has improved dramatically in Turkey within the past five years. In the REALITY-HF study, the results of which were published in 2014, the rates of RAS inhibitor, be-

ta-blocker, and MRA use were 68%, 79%, and 34%, respectively, in the outpatient population with HFrEF (17). In the TAKTİK study, the rates of RAS inhibitor, beta-blocker, and MRA use during hospitalization were 60%, 46%, and 40%, respectively, in patients diagnosed with acute decompensated HF, whereas the same rates were found to be 78%, 90%, and 55%, respectively, in our study (18).

The most important advantage of the ATA study as compared with previous studies on HF treatment conducted in Turkey is that the ATA study revealed detailed data on doses in addition to those on the rates of drug utilization. Although the rates of RAS inhibitor and beta-blocker treatment use are satisfactory, the number of patients treated with target doses is far from optimal. The results of our study suggest that the proportion of patients receiving RAS inhibitor treatment at the target dose is low in general. Although three-quarters of the patient population had a blood pressure of ≥ 110 mm Hg, the proportion of patients receiving a RAS inhibitor at the target dose was only 24%. Similarly, more than 90% of patients do not receive the target beta-blocker dose. These real-life data confirm the results obtained in other registry studies (1, 7, 15, 19, 20). There are significant differences between the doses administered to patients with HFrEF in daily clinical practice and those administered in selected patient populations included in randomized controlled clinical trials. In randomized controlled trials, the rate of achieving the target dose ranged from 49% to 84% in patients receiving RAS inhibitors and from 66% to 80% in patients receiving beta-blockers (21–25). This considerable difference in the administration of target dose therapy between real-life and randomized controlled trial data may due to numerous reasons, including the following: (1) patient-related factors such as advanced age, frailty, and the presence of multiple comorbidities leading to high-dose intolerance; (2) physician-related factors such as lack of awareness about the dose targets in treatments, reluctance and lack of motivation in terms of dose up-titration, a focus on eliminating symptoms rather than on reducing mortality, or fear of side effects; and (3) nonmedical factors such as the cost of medications, legislation on reimbursement for medications, and restriction of access to health care services (6, 7). In the ATA study, conditions causing high-dose intolerance such as symptomatic hypotension and/or bradycardia as well as deterioration of renal functions or hyperkalemia were detected in approximately half of the patients who did not receive treatment at the target dose. In the other half of the patients who did not receive treatment at the target dose, we concluded that no dose up-titration was performed by physicians, although there were no contraindications or causes of intolerance. This result suggests that physicians are not sufficiently aware of dose targets, do not have insufficient motivation for dose up-titration, or do not perform dose up-titration because of the risk of side effects.

In terms of device therapies, we found that approximately one-fifth of patients in our study population who had indications for

ICD treatment and approximately one-third of patients who had indications for CRT received these therapies. We determined that most patients who did not receive device treatments were not recommended this treatment option by their physician, although they were eligible. These results suggest that physicians do not adequately investigate patients with chronic HFrEF in terms of ICD or CRT requirement or prefer more conservative treatment options because of financial and cost-effectiveness concerns.

Study limitations

The main limitation of the ATA study is its observational design, which may have led to bias through confounding by demographical and clinical variables that were not controlled for. The entire study population was obtained from the cardiology outpatient clinic, and this population did not include those presenting at the internal medicine and/or family medicine outpatient clinics. Thus, patients included in the ATA study do not represent the entirety of patients with HFrEF. Although the ATA study was conducted in seven geographical regions of Turkey, some geographic areas may have been underrepresented. Thus, the study population does not represent the general population in Turkey. Registry data were based on the documentation of medical history and treatments during the first outpatient clinic visit, and follow-up data were not obtained. Therefore, the rehospitalization and mortality rates of the patients after the first visit are unknown. Because of these limitations, the results of this study should be interpreted carefully.

Conclusion

The data collected in the ATA study show that the use of RAS inhibitors and beta-blockers-but not MRAs and ivabradin-in patients with chronic HFrEF can be considered acceptably adherent to the recommendations of HF guidelines. Although the rates of RAS inhibitor and beta-blocker treatment use are satisfactory, the number of patients treated with target doses is far from optimal. Similarly, with respect to device implantation, there is a big gap between the recommendations of current HF guidelines and daily clinical practice.

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