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Prognostic Significance of Statins in Ischemic and Non-ischemic Heart Failure Patients with Reduced Ejection Fraction in Real Life

Ejeksiyon Fraksiyonu Azalmış İskemik ve İskemik Olmayan Kalp Yetersizliği Hastalarında Statinlerin Gerçek Hayattaki Prognostik Önemi

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Objective: Although the positive effects of statin therapy in cardiovascular diseases are known, current heart failure guidelines do not recommend statins. The aim of this study was to investigate the effect of statin on all-cause mortality in patients with ischemic or non-ischemic heart failure with low ejection fraction using real-life data.

Methods: In this study, 1144 patients with heart failure with low ejection fraction were included retrospectively.

Results: In the study cohort, 55.4% were ischemic heart failure patients and 42.4% of the patients were on statin therapy. The rate of patients using statins was 60.5% in the ischemic group and 20.2% in the non-ischemic group ($P < .001$). During the median 35-month follow-up, 337 deaths were observed. Mortality rates were similar in ischemic and non-ischemic groups (31.3% vs 26.9%, $P = .092$). When the statin usage status of the patients was examined, ischemic heart failure, all survivors, and survivors with ischemic heart failure were using statins at a higher rate ($P < .001$). In the Kaplan–Meier analysis of all patients, the mortality rate was 22.7% in statin users, while the mortality rate was significantly higher in those who did not use statins, 34.4% ($P < .001$). All-cause mortality was significantly higher in patients with ischemic heart failure not using statins than in patients using statins ($P < .001$) but not in non-ischemic heart failure ($P = .07$). Using statin was an independent predictor of all-cause mortality in all patients (hazard ratio: 0.661, 95% CI: 0.518-0.843, $P = .001$) and ischemic heart failure patients (hazard ratio: 0.618, 95% CI: 0.456-0.838, $P = .002$).

Conclusion: Since statin use reduces all-cause mortality in patients with ischemic heart failure, it may be recommended to continue statin therapy.

Keywords: All-cause mortality, heart failure, ischemic, non-ischemic, statin

ÖZET

Amaç: Statin tedavisinin kardiyovasküler hastalıklarda olumlu etkileri bilinse de mevcut kalp yetersizliği (KY) kılavuzları statinleri önermemektedir. Amacımız, düşük ejeksiyon fraksiyonlu (DEFKY) iskemik ve iskemik olmayan KY hastalarında statinin tüm nedenlere bağlı mortalite üzerindeki etkisini gerçek yaşam verileri ile araştırmaktır.

Yöntemler: Çalışmaya DEFKY'li 1144 hasta retrospektif dahil edildi.

Bulgular: Bu kohortta hastaların %55,4'ü iskemik KY idi. Statin kullanan hastalar çalışma grubunun %42,4'ünü oluşturmaktaydı. Statin kullanan hasta oranı iskemik grupta %60,5, iskemik olmayan grupta %20,2 idi ($P <$,001). Median 35 aylık takipte 337 ölüm gözlendi. Mortalite oranları iskemik ve iskemik olmayan gruplarda benzerdi (%31,3'e %26,9, $P =$,092). Hastaların statin kullanım durumları incelendiğinde; tüm iskemik KY hastalarında, tüm sağ kalanlarda ve iskemik KY olup sağ kalanlarda daha yüksek oranda statin kullanılmaktaydı ($P <$,001). Kaplan-Meier analizinde tüm hastalarda, statin kullananlarda ölüm oranı %22,7 iken, statin kullanmayanlarda ölüm oranı %34,4, anlamlı olarak daha yüksekti ($P <$,001). Tüm nedenlere bağlı mortalite statin kullanmayan iskemik KY hastalarında, statin kullanan hastalara göre anlamlı olarak daha yüksekti ($P <$,001), ancak iskemik olmayan KY'de değildi ($P =$,07). Statin kullanımı, tüm hastalarda (HR: 0,661, 95% CI: 0,518-0,843, $P =$,001) ve iskemik KY hastalarında (HR: 0,618, 95% CI: 0,456-0,838, $P =$,002) tüm nedenlere bağlı mortalitenin bağımsız bir öngörücüsüydü.

Sonuç: İskemik KY hastalarında statin kullanımı tüm nedenlere bağlı mortaliteyi azalttığından tedaviye devam edilmesi önerilebilir.

Anahtar Kelimeler: İskemik, kalp yetersizliği, noniskemik, statin, tüm nedenlerden ölüm

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Heart failure (HF) represents a major public health problem with an increasing prevalence, affecting at least 23 million people worldwide.[1] Guidelines for medical therapy include the use of angiotensin-converting enzyme inhibitors, beta-blockers, aldosterone antagonists, angiotensin receptor/neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 inhibitors, as well as implantable cardioverter-defibrillators or cardiac resynchronization therapy (ICD or CRT). Despite all the treatments, HF remains an important cause of morbidity and mortality. Although statin therapy is assumed to have potential benefits in cardiovascular disease, current guidelines do not recommend statins for the treatment of HF.[2]

Two large, randomized controlled trials and a comprehensive meta-analysis involving HF patients with reduced ejection fraction (HFrEF) showed no benefit of statin therapy on cardiovascular mortality.[3,4] A small reduction in hospitalizations and myocardial infarction in HF was demonstrated with the use of statins.[5-7] Based on available evidence, routine administration of statins in patients with HF is not recommended without other indications for their use, such as in coronary artery disease (CAD).[2] However, most HF patients have been prescribed statins for any reason. Whatever the indication and etiology of HF, its effect on real-life outcomes is unknown.

Our study aims to examine the relationship between statin use and all-cause mortality in ischemic and non-ischemic HFrEF, regardless of statin type and dose, using real-life data.

Methods

Ischemic and non-ischemic HFrEF patients admitted to Antalya Training and Research Hospital outpatient clinic between October 2015 and May 2020 were retrospectively evaluated. Of the 1392 patients, 1144 patients who were known to use statins and whose mortality information could be accessed from the hospital database were included in the study. This study complies with the rules of the Declaration of Helsinki (2013), and it was approved by the Antalya Training and Research Hospital ethics committee. Inclusion criteria are as follows: (i) a diagnosis of HF, (ii) with a left ventricular ejection fraction (LVEF) of ≤40%, (iii) age ≥ 18 years, and (iv) known to use statins. The diagnosis of HF was made based on the European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF.[2]

ABBREVIATIONS

ACE-I/ARBs	Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers
ARNIs	Angiotensin receptor/neprilysin inhibitors
CAD	Coronary artery disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CRT	Cardiac resynchronization therapy
eGFR	Estimated glomerular filtration rate
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
HFrEF	HF patients with reduced ejection fraction
HR	Hazard ratios
ICD	Implantable cardioverter-defibrillators
IQR	Interquartile ranges
LVEF	Left ventricular ejection fraction
LDL-C	Lipoprotein cholesterol
NYHA	New York Heart Association
NT-proBNP	N-terminal pro-brain natriuretic peptide

Data including demographics, medical history, results from physical examination, electrocardiogram, echocardiography, current medications, laboratory test results, and all-cause mortality were collected retrospectively from the hospital clinical database. The patients were divided into 2 groups: ischemic and non-ischemic HF, and their baseline characteristics were compared. The ischemic group consisted of patients with obstructive coronary heart disease with coronary stenosis greater than 50% by coronary angiography. The non-ischemic group was determined as the group without obstructive CAD. All parameters were measured using standard methods. The estimated glomerular filtration rate (eGFR) was calculated using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

The endpoint of this study was all-cause mortality in patients with ischemic and non-ischemic HFrEF, using and not using statins.

Statistical Analysis

Normality was assessed using the Kolmogorov–Smirnov test. Normally distributed data were expressed as means with standard deviations and analyzed using Student's *t*-test. Non-normally distributed data were expressed as medians with interquartile ranges [IQR, 25%-75%] and analyzed using Mann–Whitney *U* test for continuous variables conformed to a non-normal distribution and the chi-square test for categorical variables. Categorical variables were reported as counts and percentages. Kaplan–Meier survival analysis with log-rank test was used to compare survival between the groups for all-cause mortality. The multivariate Cox regression analysis was performed to define independent predictors of all-cause mortality. Among the parameters included in the Cox regression model, parameters with a significant *P*-value in the univariate regression analysis were included in the multivariate regression analysis. Results are presented as hazard ratios (HR) with 95% CI. A *P*-value of .05 was considered statistically significant. Statistical Package for the Social Sciences software v. 22.0 (IBM Corp.; Armonk, NY, USA) was used for statistical analyses.

Results

Study Population Characteristics

The cohort comprised 1144 patients; 71.7% male and 28.3% female, and the median age was 64 years [IQR, 55-73]. The median LVEF was 30% [IQR, 25-35], and 42.8% of patients were in the functional class New York Heart Association (NYHA) II and 24.5% were in NYHA III or IV. In this cohort, 55.4% were ischemic HF patients and 44.6% were non-ischemic HF patients The patients who were on statin therapy constituted 42.4% of the study group. In this cohort, 39.8% of patients had diabetes, 53.4% had hypertension, 50.4% had CAD, and 38.6% had hyperlipidemia. The rates of use of drugs that reduce mortality as recommended by HF guidelines for angiotensin-converti ng enzyme inhibitors or angiotensin receptor blockers (ACE-I/ARBs), beta-blockers, and aldosterone antagonists were 80.5%, 92.7%, and 69.5%, respectively. Also, ICD or CRT was applied to only 13.7% of the patients. Median total cholesterol was 167 mg/dL [IQR, 136-204], median low-density lipoprotein cholesterol (LDL-C) was 96 mg/dL [IQR, 71-127], median high-density lipoprotein cholesterol (HDL-C) was 42 mg/dL [IQR,36-50], and median triglyceride was 118 mg/dL [IQR,84-170]. Table 1 shows the baseline characteristics of the population.

Table 1. Baseline Characteristics of Patients with Ischemic and Non-ischemic Heart Failure

Characteristics	Total (n=1144)	Ischemic (n=634)	Non-ischemic (n=510)	*P*
Age (years)	64 (55-73)	65 (56-73)	63 (52-72)	<.001
Male, n (%)	820 (71.7)	502 (79.2)	318 (62.4)	<.001
Female, n (%)	324 (28.3)	132 (20.8)	192 (37.6)	
BMI (kg/m²)	26.6 (23.6-30)	26.4 (23.8-29.7)	26.8 (23.5-30.5)	.435
HF duration (months)	12 (2-60)	23.5 (4-60)	10 (2-48)	<.001
Medical history				
Diabetes, n (%)	455 (39.8)	293 (46.2)	162 (1.8)	<.001
Hypertension, n (%)	611 (53.4)	357 (56.3)	254 (49.8)	.028
Hyperlipidemia, n (%)*	442 (38.6)	329 (51.9)	113 (22.2)	<.001
Chronic kidney disease, n (%)	175 (15.3)	112 (17.7)	63 (12.4)	.013
Chronic obstructive pulmonary disease, n (%)	187 (16.3)	112 (17.7)	75 (14.7)	.178
Peripheral vascular disease, n (%)	30 (2.6)	25 (3.9)	5 (1)	.002
Previous coronary artery disease, n (%)	577 (50.4)	563 (88.8)	14 (2.7)	<.001
Previous coronary artery bypass, n (%)	220 (19.2)	218 (34.4)	2 (0.4)	<.001
Previous percutaneous coronary intervention, n (%)	407 (35.6)	394 (62.1)	13 (2.5)	<.001
Smoking (past/present), n (%)	352 (30.8)	226 (35.7)	126 (24,7)	<.001
Medication				
ACE-I/ARB, n (%)	921 (80.5)	512 (80.8)	409 (80.2)	.812
Beta-blockers, n (%)	1060 (92.7)	592 (93.4)	468 (91.8)	.299
Aldosterone antagonist, n (%)	795 (69.5)	415 (65.5)	380 (74.5)	.001
Statin, n (%)	485 (42.4)	382(60.5)	103 (20.2)	<.001
Acetylsalicylic acid, n (%)	665 (58.1)	456 (71.9)	209 (41)	<.001
Other antiaggregants, n (%)	313 (27.4)	273 (43.1)	40 (7.8)	<.001
Loop diuretics, n (%)	768 (67.1)	421 (66.4)	347 (68)	.558
ARNI, n (%)	29 (2.5)	14 (2.2)	15 (3)	.648
Physical findings				
Systolic BP (mmHg)	110 (100-130)	110 8100-130)	120 (100-130)	.025
Diastolic BP (mmHg)	60 (60-80)	60 (60-70)	70 (60-80)	.012
Heart rate (b.p.m)	76 (67-86)	75 (67-85)	78 (69-91)	.001
Atrial fibrillation, n (%)	218 (19.1)	88 (13.9)	130 (25.5)	<.001
NYHA I, n (%)	374 (32.7)	195 (30.8)	179 (35.1)	.396
NYHA II, n (%)	490 (42.8)	283 (44.6)	207 (40.6)	
NYHA III or IV, n (%)	280 (24.5)	156 (24.6)	124 (24.4)	
ICD, n (%)	125 (10.9)	74 (11.7)	51 (10)	.234
CRT, n (%)	32 (2.8)	13 (2.1)	19 (3.7)	
Echocardiographic data				
LVEF (%)	30 (25-35)	30 (25-35)	30 (25-35)	.421
LV EDD (mm)	58 (53-63)	57 (52-63)	58 (53-64)	.067
LV ESD (mm)	47 (42-54)	47 (41-54)	48(43-55)	.028
Laboratory data				
Fasting blood glucose (mg/dL)	106 (91-139)	109 (92-151)	102 (89-126)	<.001
Creatinine (mg/dL)	1.11 (0.96-1.36)	1.15 (0.99-1.39)	1.05 (0.91-1.31)	<.001

(*Continued*)

Table 1. Baseline Characteristics of Patients with Ischemic and Non-ischemic Heart Failure (*Continued*)

Characteristics	Total (n=1144)	Ischemic (n=634)	Non-ischemic (n=510)	*P*
eGFR (mL/min/1.73 m²)	64.8 (49.5-80.4)	63.2 (48.7-77.4)	67.2 (50.5-84.5)	.001
Total cholesterol (mg/dL)	167 (136-204)	160 (131-193)	177 (143-214)	<.001
LDL cholesterol (mg/dL)	96 (71-127)	160 (131-193)	177 (143-214)	<.001
HDL cholesterol (mg/dL)	42 (36-50)	40 (34-48)	44 (37-52)	<.001
Triglyceride (mg/dL)	118 (84-170)	118 (86-168)	117 (83-172)	.523
Sodium (mmol/L)	138 (136-140)	138 (136-140)	139 (136-140)	.249
Albumin (g/dL)	4.2 (3,9-4.5)	4.2 (3.8-4.5)	4.2 (3.9-4.5)	.247
Hemoglobin (g/dL)	13.1 (11.6-14.5)	13.1 (11.6-14.4)	13.2 (11.8-14.5)	.423
NT-proBNP (ng/L)	1832 (694-4518)	1937 (711-4771)	1775 (637-4212)	.295
High-sensitive troponin T (ng/L)	22 (12-36)	24.5 (13-40.2)	18 (10-34)	.001
CRP (mg/dL)	5 (2-11)	5 (2-11)	5 (2-11)	.359

All numerical data are expressed as the median (25%-75% interquartile range). The *P* values between the ischemic and non-ischemic patients were determined using the Mann–Whitney *U*-test or the χ^2 test.
*Patient-reported history of hypercholesterolemia.
HF, heart failure; BMI, body mass index; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; BP, blood pressure; b.p.m., beats per minute; NYHA, New York Heart Association; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LV EDD, left ventricular end-diastolic diameter; LV ESD, left ventricular end-systolic diameter; eGFR, estimated glomerular filtration rate; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein.

Etiologies of Heart Failure and Baseline Characteristics

A comparison of baseline characteristics of patients with ischemic and non-ischemic HFrEF is shown in Table 1. Patients with ischemic HF were older, mostly men, and had a longer HF duration (all, $P<.001$). The rate of diabetes, hyperlipidemia, chronic kidney disease, and peripheral vascular disease was significantly higher in ischemic HF patients ($P<.001$, $P<.001$, $P=.013$, $P=.002$, respectively). In total, 34.4% of the ischemic HF patients had a history of previous coronary artery bypass and 62.1% had a history of previous percutaneous coronary intervention. The rate of smokers or ex-smokers was 35.7%, and it was higher in ischemic HF ($P<.001$). The rates of use of ACE-I/ARBs, beta-blockers, aldosterone antagonists, and ARNIs were similar in both groups. The rate of patients using statins was 60.5% in the ischemic group and 20.2% in the non-ischemic group ($P<.001$). The use of acetylsalicylic acid and other antiaggregants was also higher in the ischemic group ($P<.001$). Systolic and diastolic blood pressure, heart rate, and atrial fibrillation rate were higher in non-ischemic HF patients ($P=.025$, $P=.012$, $P=.001$, $P<.001$, respectively). NYHA classes and LVEF were similar between groups, but left ventricular end-systolic diameters were greater in non-ischemic HF patients ($P=.028$). Laboratory workup indicated that fasting blood glucose, creatinine, and high-sensitive troponin T values were significantly higher ($P<.001$, $P<.001$, respectively), and eGFR was lower in the ischemic HF group ($P=.001$). Total cholesterol, LDL-C, and HDL-C values were higher in the non-ischemic HF group (all, $P<.001$). N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were similar in both groups ($P=.295$).

The Relationship Between Statin Use and Mortality

With a follow-up of median of 35 months [IQR, 26-49], all-cause mortality was 29.5% (n=337). Mortality rates were 26.9% (n=137) in the non-ischemic group and 31.3% (n=200) in the ischemic group ($P=.092$). The status of statin use in patient groups is shown in Figure 1. Accordingly, the rate of statin use was significantly higher in ischemic HF patients, all survivors, and survivors with ischemic HF (all, $P<.001$). However, there was no difference in statin use in survivors and non-survivors with non-ischemic HF ($P=.056$) (Figure 1). About 36.8% of NYHA III-IV patients were using statins. In NYHA III-IV patients, all-cause mortality was lower in patients who use statins than those who did not use statins (38.8% vs 55.4%, $P=.008$).

The relationship between all-cause mortality and statin use in all patients was evaluated by Kaplan–Meier analysis. While the mortality rate was 22.7% in patients using statins, the mortality rate was significantly higher in those who did not use statins at 34.4% in all patients ($P<.001$, log-rank test) (Figure 2A). All-cause mortality was significantly higher in ischemic HF patients who did not use statins than in patients who use statins (43.7% and 23.6%, respectively, $P<.001$, log-rank test) (Figure 2B). However, no difference was found in all-cause mortality in non-ischemic HF patients who were using and not using statins (19.4% and 28.7%, respectively, $P=.072$, log-rank test) (Figure 2C). The multivariate Cox regression model identified that using statin was an independent predictor of all-cause mortality in all patients (HR: 0.661, 95% CI: 0.518-0.843, $P=.001$) (Table 2). Other parameters associated with mortality were the use of statin and ACE-I/ARB, hemoglobin, eGFR, sodium, and triglyceride in the multivariate analysis (Table 2). In addition, statin use was an independent predictor of all-cause mortality in ischemic HF (HR: 0.618, 95% CI: 0.456-0.838, $P=.002$) but not in non-ischemic HF (HR: 0.616, CI: 0.376-1.009, $P=.054$) (Table 3).

Discussion

The rates of ischemic and non-ischemic HFrEF patients were similar in our study. About 42.4% of patients were using statin. Statin use was significantly higher in patients with ischemic HF

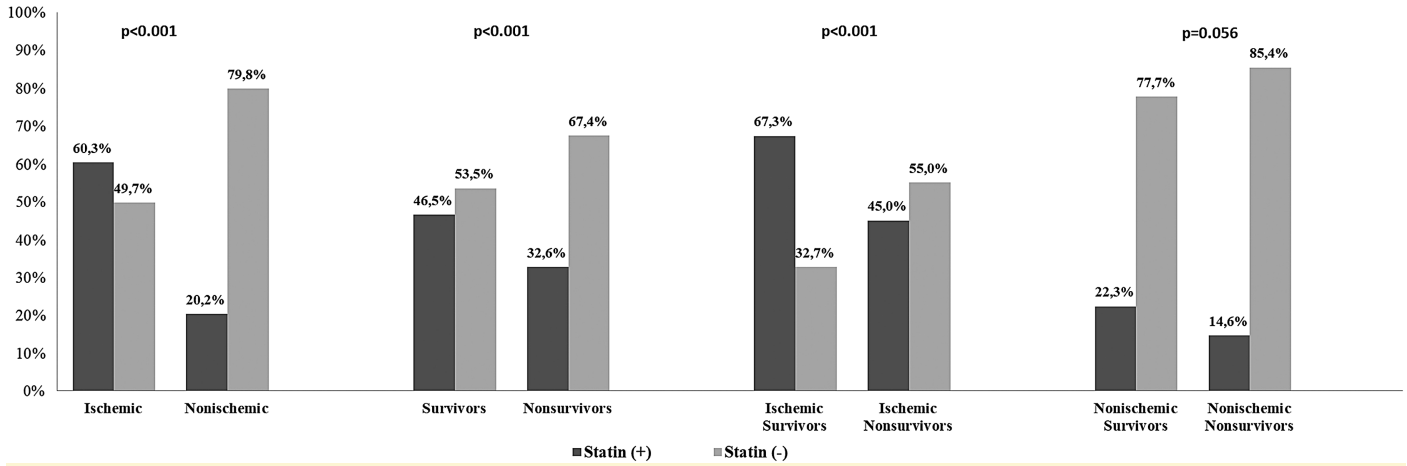

Figure 1. Comparison of patient groups according to statin use.

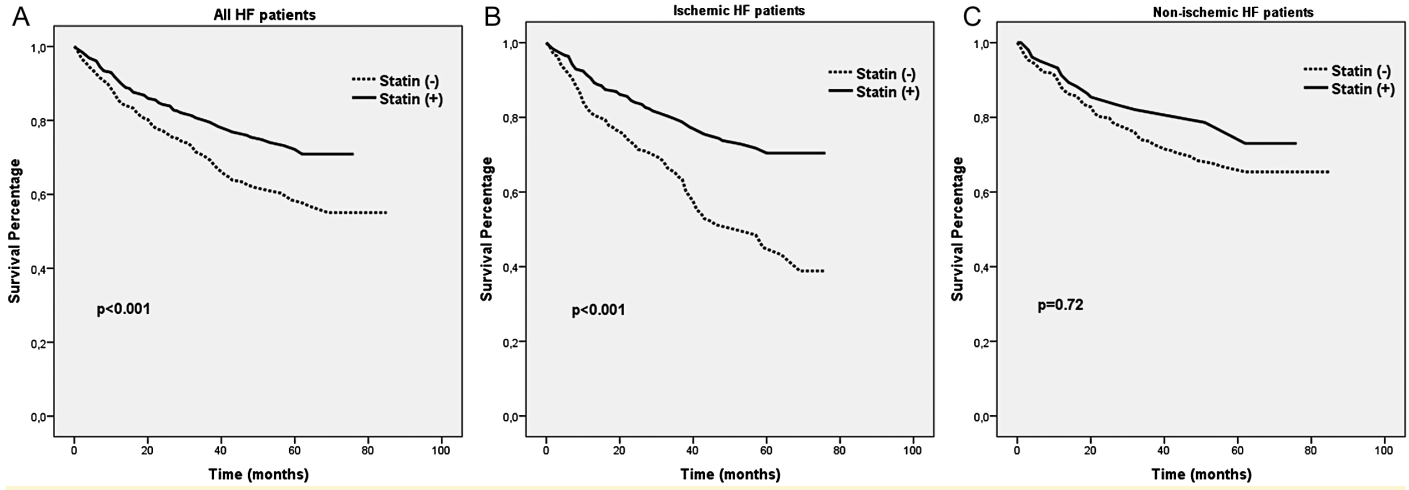

Figure 2. A-C. Kaplan–Meier curves for time to all-cause mortality in all patients (A), ischemic HF patients (B), and non-ischemic HF patients (C). HF, heart failure.

Table 2. Univariate and Multivariate Analysis for All-Cause Mortality in All Heart Failure Patients

	Univariate Analysis		Multivariate Analysis	
Variables	**Hazard Ratio (95% CI)**	***P***	**Hazard Ratio (95% CI)**	***P***
Statin	0.616 (0.491-0.774)	<.001	0.661 (0.518-0.843)	.001
ACE-I/ARB	0.452 (0.359-0.569)	<.001	0.694 (0.533-0.904)	.007
Beta-blockers	0.702 (0.480-1.029)	.07		
Aldosterone antagonist	0.750 (0.600-0.937)	.011	1.008 (0.784-1.296)	.95
LVEF	0.981 (0.966-0.996)	.012	0.984 (0.970-0.999)	.39
Hemoglobin	0.775 (0.732-0.820)	<.001	0.875 (0.823-0.930)	<.001
eGFR	0.979 (0.974-0.984)	<.001	0.987 (0.982-0.993)	<.001
Sodium	0.936 (0.914-959)	<.001	0.960 (0.937-0.984)	.001
Total cholesterol	0.995 (0.993-0.998)	<.001	0.999 (0.999-1.003)	.705
LDL cholesterol	0.997 (0.995 -1.000)	.045		
HDL cholesterol	0.987 (0.978-0.997)	.011	0.990 (0.979-1.002)	.91
Triglyceride	0.995 (0.993-.0996)	<.001	0.996 (0.994-0.998)	<.001

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 3. Multivariate Analysis for All-Cause Mortality in Ischemic and Non-ischemic Heart Failure Patients

	Ischemic HF		Non-ischemic HF	
Variables	**Hazard Ratio (95% CI)**	***P***	**Hazard Ratio (95% CI)**	***P***
Statin	0.618 (0.456-0.838)	.002	0.616 (0.376-1.009)	.054
ACE-I/ARB	0.761 (0.543-1.065)	.111	0.567 (0.373-0.863)	.008
Aldosterone antagonist	1.059 (0.771-1.454)	.723	1.047 (0.693-1.583)	.828
LVEF	0.980 (0.960-1.000)	.045	0.989 (0.966-1.013)	.371
Hemoglobin	0.857(0.789-0.930)	<.001	0.900 (0.819-0.990)	.03
eGFR	0.982 (0.975-0.990)	<.001	0.993 (0.986-1.001)	.106
Sodium	0.951 (0.924-0.979)	.001	0.988 (0.940-1.038)	.634
Total cholesterol	1.000 (0.996-1.004)	.962	0.999 (0.994-1.005)	.83
HDL cholesterol	1.000 (0.986-1.013)	.949	0.979 (0.961-0.999)	.037
Triglyceride	0.998 (0.995-1.000)	.037	0.993 (0.990-0.997)	<.001

HF, heart failure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

(60.5%), and only 20.2% of patients with non-ischemic HF were using statin. All-cause mortality rates were similar in both groups. However, at a median follow-up of 35 months, all-cause mortality was significantly lower in all patients using statins, and this association was demonstrated in ischemic HF but not in non-ischemic HF. In addition, statins have been shown to independently reduce all-cause mortality in patients with ischemic HF in real life.

Statins are the cornerstone of medical therapy for the prevention and treatment of CAD and have shown consistent cardiovascular benefits in numerous large studies.[8,9] However, although the guidelines recommend the use of statins for the prevention of multiple primary and secondary cardiovascular diseases, they do not make any recommendations regarding the use of statins in patients with HF.

Two large prospective randomized studies failed to confirm the beneficial effects of statins in patients with HF. In the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study, 5011 NYHA class II-IV patients (age ≥ 60 years) with ischemic systolic HF were randomized to rosuvastatin 10 mg or placebo. In this study, during a median follow-up of 32.8 months, rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in elderly patients with systolic HF but reduced the number of cardiovascular hospitalizations.[3] However, a CORONA subgroup study significantly reduced the rate of hospitalization for recurrent HF by 15%-20% in the rosuvastatin group.[6] In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-HF study, 4574 patients with NYHA class II to IV chronic HF were randomized to rosuvastatin 10 mg or placebo, and 40% of patients had ischemic cardiomyopathy. Similar efficacy to placebo was observed in all outcomes including cardiovascular mortality, ischemic endpoints, and admissions for HF.[4] Thus, despite retrospective analyses and small studies demonstrating the beneficial effects of statins in patients with HF, 2 large, well-conducted, prospective, randomized studies demonstrated that statin therapy did not provide significant clinical benefit in patients with HF of ischemic or non-ischemic origin. In our study, both ischemic and non-ischemic groups were evaluated similar to the GISSI-HF study. However, unlike the results of this study, we found that the use of statins reduces all-cause mortality only in patients with ischemic HF. In addition, this effect was independent of cholesterol levels and other drugs that reduce mortality in HF (HR: 0.618, 95% CI: 0.456-0.838, *P* = .002).

A meta-analysis of 11 retrospective and 2 prospective studies showed a 26% reduction in mortality in HF patients with statin therapy (HR: 0.74; 95% CI 0.68-0.8).[10] Statin use reduced all-cause mortality by 34% in all patients in our study (HR: 0.661, 95% CI: 0.518-0.843, *P* = .001). Eight of the 13 studies included ischemic and non-ischemic HF. A separate analysis demonstrated a similar protective effect of statins in HF patients, regardless of etiology (ischemic HF and non-ischemic HF, HR: 0.73; 95% CI 0.65-0.82 vs HR: 0.73; 95% CI 0.61-0.87, respectively).[10] Despite limitations such as the fact that most of the studies included in the meta-analysis were retrospective analyses, there was no complete randomization in the studies, and differences in follow-up times, statins used, and dose, and these meta-analysis results showed that patients with HF demonstrated that statins would provide benefit in patients regardless of the underlying cause. We have seen that the beneficial effects of statins on mortality originate from the ischemic group when the ischemic and non-ischemic groups are separated. While there was a significant 39% reduction in all-cause mortality in ischemic HF, it was similar in the non-ischemic group with and without statin users (HR: 0.618, 95% CI: 0.456-0.838, *P* = .002; HR: 0.616, CI: 0.376-1.009, *P* = .054; respectively). While the rates of non-statin users were higher in the studies evaluated in the meta-analysis, the rate of statin use in non-ischemic HF was only 20% in our study. If this rate was higher, we wonder if the result would have changed. A study done in the Swedish Heart Failure Registry may be the answer. The association between statin use and clinical outcome in HFrEF patients was recently detailed in an unselected propensity score-matched cohort study.[11] In this study, statin use was associated with a reduction in all-cause

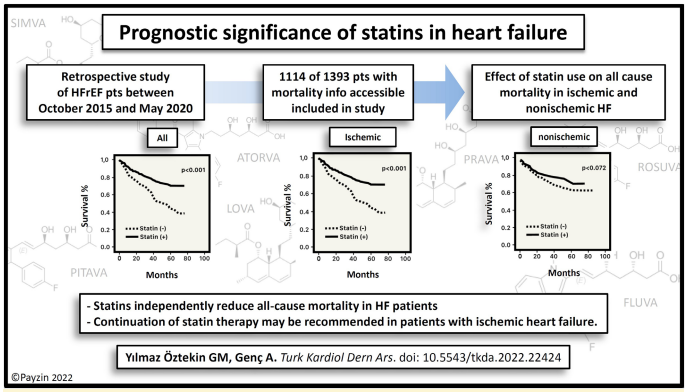

Figure 3. A visual summary of the article.

and cardiovascular 1-year mortality and HF hospitalization (HR: 0.81, 95% CI: 0.76-0.86; HR: 0.80, 95% CI: 0.75-0.87; HR: 0.92, 95% CI: 0.86-0.97;, all $P < .005$, respectively). A strong interaction was demonstrated between the use of statins and the presence of ischemic heart disease for all-cause mortality (HR: 0.76, 95% CI: 0.70-0.82, $P < .001$). This association was absent in those without ischemic heart disease (HR: 0.95, 95% CI: 0.85-1.07, $P = .430$).

First of all, this is a retrospective observational study. Regardless of the type of statin used and the dose, it was questioned whether the patients used statins or not, and the effect of using any statin at any dose on ischemic and non-ischemic HF all-cause mortality was examined. Therefore, this study does not provide conclusions about the effective dose of statin and the type of statin. In addition, since the rate of use of statins in non-ischemic HF is lower than the rate of use in ischemic HF in our study, it is not known whether the same results will be obtained in non-ischemic HF even if the rate of use is higher. Since the death status of the patients was evaluated from the hospital records, the causes of death could not be reached clearly. Therefore, the results were evaluated as all-cause death. The effect of statin on mortality in HF with preserved EF is unknown, as it has been evaluated in patients with HFrEF.

Conclusion

Statin therapy is not necessary for patients with non-ischemic HF, as HF guidelines recommend, as it does not alter mortality. Statins independently reduce all-cause mortality in patients with ischemic heart failure in real life. Therefore, considering the effect on all-cause mortality in ischemic HF, it may be recommended to continue statin therapy.

Visual summary of the article can be seen in Figure 3.

Ethics Committee Approval: The study was approved by the medical ethics committee of Antalya Training and Research Hospital (16/09/2021, No: 14/13).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors declare that they have no competing interest.

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