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The effect of achieving guideline-based target low-density lipoprotein cholesterol levels on mortality in transcatheter aortic valve implantation patients with coronary artery disease

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ABSTRACT

Objectives: The aim of this retrospective study was to evaluate the effects of bringing low-density lipoprotein cholesterol (LDL-C) values to levels in line with guideline recommendations on long-term mortality in patients with a known history of coronary artery disease (CAD), undergoing transcatheter aortic valve implantation (TAVI), and long-term pre-treatment with statins.

Methods: This is a retrospective and observational study of patients undergoing TAVI at a tertiary heart center with a history of CAD and long-term statin therapy. Ninety-nine patients were included in the study. The relationship between LDL-C levels in accordance with the guidelines and 5-year mortality was determined by regression analysis.

Results: When the study population was divided into 2 groups with and without 5-year mortality, LDL-C values were found to be significantly higher in the mortality group (120 mg/dL vs. 93.9 mg/dL, $p < 0.001$). Parameters associated with the development of 5-year mortality were evaluated with univariate and multivariate logistic regression analysis. LDL-C ≥ 100 mg/dL (OR: 6.59, 95% CI: 2.17-20.01) and LDL-C ≥ 70 mg/dL (OR:3.88, 95% CI: 1.16-12.93) parameters were determined as independent predictors of mortality independent of other parameters.

Conclusions: The most important result obtained in this study is that achieving the LDL-C level targets specified in the guidelines significantly reduces the in-hospital and 5-year mortality rates in patients with a previous history of CAD and statin use and undergoing TAVI. Although all patients included in the study used statins, the mortality rate was significantly higher in patients who did not reach the target LDL-C value.

Keywords: Transcatheter aortic valve implantation, low-density lipoprotein cholesterol, statin, coronary artery disease

Severe aortic stenosis (AS) may result from rheumatic heart disease or, more commonly, from calcification of the congenital bicuspid or three-leaf aortic valve [1]. The prevalence of AS increases with age, while it is around 0.2% at younger ages, it rises to 9.8% after the age of 80 [1]. AS is the most common

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indication for surgical heart valve replacement in many countries. In patients who are not suitable for surgery, transcatheter aortic valve implantation (TAVI) is now an established and safe treatment option that continues to evolve [2, 3].

Despite its minimally invasive nature, TAVI is always associated with numerous complications that may affect outcomes in elderly patients. It is very important to identify patients likely to benefit from TAVI. Although procedural outcomes have improved significantly thanks to increased operator experience and progressive improvements in TAVI devices, to date there is no satisfactory TAVI risk score that can determine individual prognosis in patients undergoing TAVI (post-TAVI patients). Studies are continuing to develop new risk score systems specific to TAVI in order to predict and reduce complications. To date, the prognostic significance of various clinical and laboratory parameters such as chronic pulmonary obstructive disease, chronic kidney disease, frailty, pulmonary hypertension, serum albumin levels, and red cell distribution width (RDW) have been demonstrated in patients undergoing TAVI [4-6].

The coexistence of AS and coronary artery disease (CAD) is frequently observed [7]. The coexistence of these two diseases can be attributed to similar risk factors and pathophysiology of the diseases [8-10]. The prevalence of CAD in severe AS ranges from 30% to 50% and increases with age [11, 12].

Statins are widely used for primary and secondary prevention of atherosclerotic cardiovascular diseases and coronary artery disease and have been shown to be associated with lower mortality rates. In addition to their lipid-lowering properties, statins have been shown to have pleotropic effects such as improving endothelial function and anti-inflammatory effects [13]. In a previous multicenter study, statin therapy was shown to reduce mortality in TAVI patients. It was found to be more effective on mortality, especially in patients with a history of coronary artery disease (CAD) and receiving treatment [14].

It has been shown in many previous randomized studies that mortality is reduced by lowering low-density lipoprotein cholesterol (LDL-C) values with statin therapy in patients with CAD [15]. In this retrospective study, we aimed to investigate the effect of bringing LDL-C values to the recommended levels in the guidelines on long-term mortality in patients with a history of CAD who underwent TAVI for severe AS and long-term use of statins.

METHODS

Study Population

This is a retrospective and observational study of patients undergoing TAVI at a tertiary heart center with a history of CAD and long-term statin therapy. All patients who met the criteria from January 2014 to January 2018 were consecutively included in the study.

The inclusion criteria used to enroll patients in the study are: (1) patients are between 20 and 90 years old, (2) having been on statin therapy for at least 6 months, (3) patients who underwent TAVI for severe aortic stenosis (4) patients who had undergone coronary artery bypass graft or percutaneous coronary intervention for severe coronary lesion before TAVI.The exclusion criteria used in the study were: (1) evidence of acute or chronic infection, (2) systemic inflammatory or autoimmune disease, (3) any history of liver disease (more than three times the upper limit of normal for liver function tests), (4) clinically any endocrine, hematological, or metabolic disease found to be significant, (5) malignancy, (6) missing clinical data for LDL-C values. 99 patients who met the current criteria were included in the study. All patients had been on statin therapy for at least 6 months and had a known history of CAD. Clinical and laboratory data of all patients were obtained from the electronic database of our hospital. The patients were scanned from the hospital database and divided into two groups according to their 5-year mortality data (mortality [+] and mortality [-] groups). Demographic characteristics, comorbidities, and laboratory characteristics of the patients were compared between those two groups. In addition, the procedural conditions of the patients were compared according to their LDL-C values (LDL-C < 100 mg/dL and LDL-C ≥ 100 mg/dL) (preprocedural, procedural, and procedural complications).

Informed consent was obtained for all cases prior to the TAVI procedure. The selection of patients with severe symptomatic AS was based on expected perioperative or short-term mortality estimated from the risk model of the European system for the cardiac operative risk assessment II (euroSCORE II) algorithm. All patients were evaluated by the multidisciplinary

heart team before the TAVI operation. Patients with severe AS were considered eligible for TAVI after they were determined to be at high or very high risk for cardiac surgery. Valve Academic Research Consortium 2 (VARC-2) criteria were used to define procedural complications [16].

Laboratory Analysis

In this study, blood samples showing hemoglobin values, white blood cell values, platelet values, and blood glucose levels were measured at admission in all patients included in the study. Low-density lipoprotein cholesterol levels were determined after 8 to 12 hours of night fasting. eGFR was calculated according to the Modification of Diet in Renal Disease formula (eGFR [mL/min/1.73 m2] = 186 × [creatinine/88.4]-1.154 × [age]- 0.203 × [0.742 female, 1.210 black]) [17].

Definitions

The term in-hospital mortality was used for deaths occurring after the procedure until the patients were discharged. The hospital's electronic database was used for 5-year mortality data. In our study, the definition of CAD included patients who had undergone previous percutaneous coronary intervention or coronary artery bypass grafting due to severe and ischemia-causing coronary artery disease. Fasting blood glucose monitoring meeting the criteria of the American Diabetes Association or using oral antidiabetic or insulin were accepted as diagnostic criteria for diabetes mellitus [18]. In the definition of stroke, transient ischemic attack (TIA) was defined if symptoms included neurologic deficit for < 24 hours. If neurological symptoms lasting longer than 24 hours were present, it was considered a stroke.

Ethics Committee Approval

All the procedures in this study including human participants were applied in compliance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and subsequent revisions or comparable ethical standards. No animals were used in this study. Approval for the study was granted by the Local Ethics Committee (Bursa Yüksek İhtisas Training and Research Clinical Research Ethics Committee, Decision no = 2011-KAEK-25 2022/11-15, Date = 02.11.2022).

Statistical Analysis

Statistical analysis of the data in this study was performed with the Statistical Package for the Social Sciences (SPSS) version 24.0 software program (IBM Corp., Armonk, NY, USA). Continuous variables were given as mean ± standard deviation (if normal distribution) and medians (interquartile ranges (IQR)) (if not normal distribution). Whether the distribution of continuous variables was close to normal was investigated with the Kolmogorov Smirnov test and the homogeneity of the variances was investigated with the Levene test. Analysis of baseline characteristics according to survival status was compared with Student's t-test or Mann-Whitney U tests. Categorical variables were analyzed with Pearson's Chi-Square test. Descriptive statistics were shown as median and interquartile range for continuous variables, and number of cases and (%) for categorical variables. Parameters that may have an effect on 5-year mortality were investigated by binary logistic regression analysis. As a result of univariate statistical analyses, the combined effects of risk factors (diabetes, contrast material amount, LDL-C level, LDL-C ≥ 70 mm/dL, and LDL-C ≥ 100 mg/dL) on mortality were evaluated. Three different models were created in which multivariate regression analysis was analyzed by adding the LDL-C parameter to the diabetes parameter as a continuous and nominal variable. As nominal variables, cut-off values were defined for the recommended values of 70 and 100 mg/dL in the guidelines. These models were evaluated separately by multivariate regression analysis. The odds ratio and 95% confidence intervals for each variable were calculated. For $p < 0.05$, the results were considered statistically significant.

RESULTS

A total of 99 patients with a previous history of CAD, using statins, and undergoing TAVI were included in the study (Median [IQR] age, 78.1 [74-84] years; 47 patients [47.5%] female). The mean follow-up period of the patients was 49.9 ± 20.1 months. In-hospital mortality was observed in 5 of the patients (5.1%) during the follow-up period. In the follow-up of the remaining 94 patients, mortality was detected in 11 patients (11.7%) after 2 years. In total, mortality was detected in 25 patients during the 5-year follow-up.

Table 1. Basic characteristics and laboratory investigations of TAVI patients by 5-year mortality status

	All patients (n = 99)	5 years mortality (-) (n = 74)	5 years mortality (+) (n = 25)	*p* value
Demographic features				
Age (years)	78.1 (74-84)	77.2 (73-83)	80,9 (76-84)	0.064
Male gender, n (%)	52 (52.5)	36 (48.6)	16 (64)	0.184
BMI	26.4 (24.3-28.1)	26,2 (24,4-27)	26.9 (24.2-29.1)	0.224
Follow-up, months	49.9 (52-62)	60.6 (60-62)	18.3 (3-29)	**< 0.001**
Comorbidities				
Hypertension, n (%)	84 (84.8)	61 (82.4)	23 (92)	0.249
Diabetes mellitus, n (%)	45 (45.5)	39 (52.7)	6 (24)	**0.013**
COPD, n (%)	16 (16.2)	10 (13.5)	6 (24)	0.218
CRF history, n (%)	26 (26.3)	20 (27)	6 (24)	0.766
Heart failure, n (%)	31 (31.3)	22 (29.7)	9 (36)	0.559
CVA history, n (%)	8 (8.1)	6 (8.1)	2 (8)	0.986
Medications				
Acetylsalicylic acid, n (%)	59 (59.6)	47 (63.5)	12 (48)	0.172
Beta blocers, n (%)	70 (70.7)	52 (70.3)	18 (72)	0.869
RAS blockers, n (%)	59 (59.6)	45 (60.8)	14 (56)	0.672
Diuretic, n (%)	40 (40.4)	31 (41.9)	9 (36)	0.604
Laboratory Values				
Hemoglobin (g/dL)	11.5 (10.4-12.7)	11.5 (10.4-12.5)	11.4 (10.3-12.8)	0.522
WBC ($\times 10^3$/mL)	8.36 (6.2-9.3)	8.54 (6.3-9.5)	7.84 (6-8.3)	0.288
Creatinine, mg/dL	1.26 (0.89-1.4)	1.21 (0.85-1.43)	1.39 (0.92-1.35)	0.869
eGFR (ml/min/1.73 m^2)	57.98 (42.2-74.3)	58,38 (42.9-74.3)	56.8 (42.2-68.7)	0.831
CRP (mg/L)	4.98 (1.6-5.7)	4.96 (1.6-5)	5.02 (1.8-6.8)	0.646
LDL-C (mg/dL)	100.5 (67-124)	93.9 (66-113)	120 (110-129)	**< 0.001**
LDL-C ≥ 70 mm/dL	66 (66.7)	45 (60.8)	21 (84)	**0.033**
LDL-C ≥ 100 mg/dL	47 (47.5)	27 (36.5)	20 (80)	**< 0.001**

Continuous variables are presented as mean ± SD or median (IQR), and nominal variables were presented as frequency (%). BMI = body mass index, COPD = chronic obstructive pulmonary disease, CRF = chronic renal failure, CVA = cerebrovascular accident, eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol, RAS = renin-angiotensin system

The median LDL-C values of the patient population were calculated as 100.5 mg/dL (67-124).

When the causes of death of the patients were examined, 2 of those who developed in-hospital mortality were due to in-hospital pneumonia. Out of 25 deaths in total, 1 patient died due to malignancy and 2 patients died due to cerebrovascular events. Of the deaths that occurred, the remaining 20 patients died from cardiovascular events (80%).

Demographic, clinical, and laboratory characteristics of patients with and without mortality in the 5-year follow-up were compared in Table 1. When comorbidities were compared between the 2 groups, the rate of diabetes was found to be significantly lower

in the group with 5-year mortality ($p = 0.013$). There was no significant difference between the 2 groups in terms of demographic characteristics, other comorbidities, and drugs used. LDL-C cholesterol values were found to be significantly higher in the mortality group (120 mg/dL vs. 93.9 mg/dL, $p < 0.001$). No significant difference was observed between other laboratory parameters. When the groups were compared in terms of duration of statin use, it was found that there was no significant difference between the duration of use in the 2 groups ($p = 0.123$).

In Table 2, the patients were divided into 2 groups with LDL-C values ≥ 100 mg/dL and < 100 mg/dL, and the preprocedural and procedural characteristics of the patients and their post-procedural complication status were compared. The amount of contrast material used during the procedure was found to be significantly higher in the group with LDL-C < 100 mg/dL ($p = 0.024$). There was no significant difference between other preprocedural and procedural characteristics. When the groups were compared in terms of complication development, in-hospital mortality ($p = 0.021$) and 5-year mortality rates ($p < 0.001$) were found to be significantly higher in the group with LDL-C ≥ 100 mg/dL. There was no significant difference between the groups in terms of other complications. In addition, when the groups were classified as LDL-C < 70 mg/dL and ≥ 70 mg/dL, 5-year mortality was found to be significantly lower in the group with LDL-C < 70 mg/dL ($p = 0.033$).

Parameters associated with the development of 5-year mortality were evaluated with univariate and multivariate logistic regression analysis. Multivariate analysis was performed in the form of 3 different models in which the LDL-C parameter was analyzed as a continuous and nominal variable for the diabetes presence parameter, which was determined to be significant by univariate analysis. Both the LDL-C ≥ 100 mg/dL predictive value (OR:6.59, 95% CI: 2.17-20.01) and the LDL-C ≥ 70 mg/dL predictive value

Tablo 2. Preprocedural and procedural characteristic and complications of all cases according to the LDL

	All patients (n = 99)	LDL-C < 100 (n = 52)	LDL-C ≥ 100 (n = 47)	*p* value
Preprocedural and procedural features				
Aortic valve area (cm^2)	0.66 ± 0.09	0.66 ± 0.1	0.66 ± 0.09	0.989
LV ejection fraction (%)	43.6 ± 13	42.3 ± 13.1	45.1 ± 12.9	0.322
EuroSCORE II, median (IOR)	30.9 (20-40.8)	30.3 (19.9-40.1)	31.7 (21-41.9)	0.385
Predilatation, n (%)	18 (18.2)	12 (23.1)	6 (12.8)	0.184
Postdilatation, n (%)	19 (19.2)	10 (19.2)	9 (19.1)	0.992
Amount of contrast agent (mL)	140.3 ± 19.6	144.1 ± 21.7	136.1 ± 16.1	**0.024**
Type of valve, n (%)				
Balloon-expandable	15 (15.2)	9 (17.3)	6 (12.8)	0.529
Self-expandable	84 (84.8)	43 (82.7)	41 (87.2)	
Complications				
Major vascular complications, n (%)	13 (13.1)	6 (11.5)	7 (14.9)	0.622
Permanent pacemaker, n (%)	14 (14.1)	6 (11.5)	8 (17)	0.434
Postprocedural IS or TIA, n (%)	4 (4)	3 (5.8)	1 (2.1)	0.358
In-hospital mortality, n (%)	5 (5.1)	0	5 (10.6)	**0.021**
5-year mortality, n (%)	25 (25.3)	5 (9.6)	20 (42.6)	**< 0.001**

Continuous variables are presented as mean ± SD or median (IQR), and nominal variables were presented as frequency (%).
IS = ischemic stroke, TIA = transit ischemic attack, LV = left ventricle

Tablo 3. Univariate and multivariate regression analysis models for determining the predictors of 5-year mortality

	Univariate odds ratio (95% CI)	*p* value	Multivariate odds ratio (95% CI)	*p* value
DM	0.28 (0.10-0.79)	**0.016**	0.31 (0.10-0.94)	**0.039**
Amount of contrast agent	1.00 (0.98-1.02)	0.937		
***LDL-C**	1.01 (1.00-1.02)	**0.021**	1.01 (1.00-1.02)	**0.044**
***LDL-C ≥ 70 mg/dL**	3.38 (1.05-10.86)	**0.041**	3.88 (1.16-12.93)	**0.027**
***LDL-C ≥ 100 mg/dL**	6.96 (2.34-20.67)	**< 0.001**	6.59 (2.17-20.01)	**0.001**

DM = diabetes mellitus, LDL-C = low-density lipoprotein cholesterol

* Tree different multivariance regression analysis models were performed on mortality in which LDL-C parameter was analyzed as a continuous and nominal variable

(OR:3.88, 95% CI: 1.16-12.93) were found to be independent predictors of 5-year mortality in multivariate analyses. When LDL-C values were evaluated in the multivariate analysis without determining the lower limit, LDL-C elevation was found to be an independent predictor of 5-year mortality (OR:1.01, 95% CI:1.00-1.02). In addition, when multivariate analysis was performed for the presence of diabetes, it was observed that the significance remained independent of other parameters (OR: 0.31, 95% CI: 0.10-0.94).

DISCUSSION

The most important result of our study is that reaching the LDL-C targets specified in the guidelines significantly reduces the risk of in-hospital and 5-year mortality in patients with a previous diagnosis of CAD, long-term use of statins, and undergoing TAVI. We found that reaching the LDL-C < 100 mg/dL targets significantly reduced the 5-year mortality rates, even after adjusting for confounding factors. To the best of our knowledge, our study is the first in the literature to show that there is a significant relationship between reaching the target LDL-C levels specified in the guideline and the 5-year mortality rate in patients with a diagnosis of CAD and undergoing TAVI.

Some previous studies have evaluated the effect of statin therapy on mortality after TAVI. Peri-Okonny *et al*. [19], using the PARTNER II and Sapien 3 clinical trials or associated registries, showed that those receiving statin therapy were associated with a reduction in 2-year all-cause, cardiovascular and non-cardiovascular mortality compared with those not receiving statin therapy. Merdler *et al*. [20] showed that high-intensity statin therapy is associated with a reduction in mortality after TAVI, using data from 1238 cases from a single-center registry. Huded *et al*. [21] also showed that high-intensity statin therapy was associated with a reduction in all-cause mortality based on 294 cases.

The underlying mechanism of statin therapy's reduction in all-cause and cardiovascular mortality risks is thought to be related to the reduction in ischemic events. [19-22]. In this study, we investigated the relationship between the effect of statin therapy, which has been shown to reduce mortality in previous studies, and LDL-C levels. The entire patient population was patients on long-term statin therapy. When we compared the patients according to the LDL-C levels recommended in the international guidelines, we found that mortality was significantly lower in patients who remained below the recommended LDL-C levels. In our study, it was observed that the 5-year mortality rate was significantly lower in patients (< 70 mg/dL) who met the LDL targets recommended for high-risk patients in the latest ESC guideline [23] ($p = 0.033$). In addition, in-hospital ($p = 0.021$) and 5-year mortality ($p < 0.001$) were found to be significantly lower in patients (< 100 mg/dL) who achieved the LDL targets recommended for intermediate-risk patients. Thus, in this study, we showed that it is necessary to closely monitor the LDL-C value in order to reduce mortality

in patients using statins, and the importance of reducing the LDL-C value to the values recommended in the guidelines.

When subgroup analyzes were performed in our study, in-hospital mortality was observed in 5 patients. When considering the 2-year mortality rate, mortality was observed in 16 patients (16.2%) at 2-year follow-up. When the causes of mortality of the patients were examined, it was observed that mortality developed from cardiovascular causes in 20 patients (%80).

In our study, mortality rates were found to be lower in patients with diabetes ($p = 0.013$). When we look at the literature on this subject, it was found that previous studies had similar results to ours. In a study by Van Nieuwkerk *et al*. [24], patients with diabetes who underwent TAVI had lower mortality rates than those without diabetes. They attributed this to the earlier development of aortic stenosis in patients with diabetes and to the application of TAVI at an earlier age. The findings of our study were found to be consistent with the literature. In addition, the follow-up period was found to be significantly lower in the group with 5-year mortality ($p < 0.001$). It is an expected result that the follow-up times are short since the patients with mortality are left to be followed up due to the mortality observed over time.

Together with these results, the effect of lowering LDL-C levels to the recommended levels in the guidelines on mortality in patients with CAD diagnosis, TAVI procedure, and chronic statin use has been demonstrated. It has been shown that lowering LDL-C levels to the levels recommended in the guidelines significantly reduces mortality. However, due to the design of our current study, prospective studies with a higher number of patients are needed to confirm our findings and study results.

Limitations

Our study had some limitations. First, the study had a retrospective and observational design, which could be accepted as the major limitation of the study. Second, this study had a small sample size. Third, the mortality data of the patients in our study were limited. We could not obtain detailed data on the causes of mortality. Finally, our findings warrant prospective and multicenter studies with larger sample sizes to elucidate the association between LDL-C levels and long-term mortality following TAVI in AS patients with CAD.

CONCLUSION

The most important result obtained in this study is that achieving the LDL-C level targets specified in the guidelines significantly reduces the in-hospital and 5-year mortality rates in patients with a previous history of CAD and statin use and undergoing TAVI. Although all patients included in the study used statins, the mortality rate was significantly higher in patients who did not reach the target LDL-C value. We found that achieving the LDL-C < 100 mg/dL targets significantly reduced the risk of in-hospital and 5-year mortality, even after adjusting for influencing factors. With these results, we showed that it is not enough to only give statin therapy to patients and that it is important to reach the guideline targets in LDL-C values in patient follow-ups.

Authors' Contribution

Study Conception: ÖFD; Study Design: ÖFD; Supervision: ÖFD; Funding: FL; Materials: FL; Data Collection and/or Processing: ÖFD; Statistical Analysis and/or Data Interpretation: ÖFD; Literature Review: ÖFD; Manuscript Preparation: ÖFD and Critical Review: FL.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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