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EVOLUTION OF BIOLOGICAL PARAMETERS IN PATIENTS WITH SEVERE AORTIC STENOSIS UNDERGOING TAVI - RESULTS AT ONE MONTH

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Abstract
Aortic stenosis is one of the most common valve diseases in patients over 60 years of age. Lack of prompt surgical correction by conventional valve replacement or interventional transcatheter aortic valve implantation (TAVI) increases the risk of morbidity and mortality, in the context of worsening clinical picture. Since the first interventional transcatheter valve implantation procedure in 2012 and to date, the evolution of technology and refinement of medical techniques has led to the refinement of the treatment method and thus to the improvement of the prognosis of patients with aortic stenosis undergoing TAVI after only one month.
Keywords: *aortic stenosis, TAVI, prognosis, biological assessment*

Rezumat
Stenoza aortică reprezintă una dintre cele mai frecvent întâlnite valvulopatii la pacienții cu vârsta de peste 60 ani. Lipsa corecției chirurgicale prompte prin înlocuire valvulară clasică, sau intervențional, prin implantare transcateter a valvei aortice (TAVI) determină creșterea riscului de morbi-mortalitate, în contextul agravării tabloului clinic. De la prima procedură intervențională de implantare a valvei transcateter în anul 2012 și până în prezent, evoluția tehnologiei și perfecționarea tehnicilor medicale a dus la rafinarea metodei de tratament și, implicit, la ameliorarea prognosticului pacienților cu stenoză aortică supuși TAVI după doar o lună.
Cuvinte cheie: *stenoză aortică, TAVI, prognostic, parametri biologici*



Internal Medicine

General Reviews

Introduction

Aortic stenosis (AS) is the most common valvular disease in industrialized countries, especially in elderly patients, causing a burden on health care systems over time through the associated financial, medical and social impact[1]. The clinical picture is dominated by a prolonged paucisymptomatic evolution culminating in the typical clinical picture which, in the absence of valve replacement (surgical or minimally invasive), is associated with a poor prognosis(2). Patients with severe, symptomatic AS who do not undergo surgical valve replacement or transcatheter aortic valve implantation (TAVI) are at high risk of morbidity and mortality, their prognosis being comparable to survival rates of some neoplasms[3-5].

Transcatheter aortic valve implantation (TAVI) is recommended in patients with moderate to severe perioperative risk assessed using risk scores as well as in the case of low-risk patients over 75 years old[6,7]. Clinical studies published to date give TAVI a superior prognosis compared to conventional surgical treatment in the short and medium term regardless of the associated risk category[8-10].

The aim of this study was to outline the clinical and biological picture of patients with severe AS undergoing TAVI and highlight the impact of this minimally invasive procedure on symptomatology and biological data at the 1-month follow-up.

Materials and methods

Study Design

We conducted a prospective study in which 86 patients diagnosed with severe aortic stenosis underwent minimally invasive valve replacement by TAVI. The diagnosis of aortic stenosis and the multimodal assessment prior to minimally invasive procedure were performed according to the current guideline recommendations using the European ESC guideline for valvular heart disease[11]. All patients with severe aortic stenosis (with aortic peak velocity above 4 m/s, with a mean gradient above 40 mmHg and an aortic valve area of less than 1 cm^2) underwent multimodal imaging evaluation by echocardiography and cardiac computed tomography for the purpose of structural and functional evaluation previously TAVI with a focus on size of the prosthesis or changes in the local anatomy. Patients with severe AS in whom classical surgical treatment was preferred or those with contraindications to minimally invasive procedures such as active endocarditis, thrombi in the ascending aorta, short distance between annulus and the coronary ostium or an annulus size smaller than 18 mm or bigger than 29 mm were excluded.

Demographics, vital signs, comorbidities, biological or echocardiographic parameters were obtained from the observation charts both at enrolment and at the one-month follow-up assessment.

Renal function assessment (creatinine and serum urea) was performed prior to TAVI, and electrocardiogram and vital parameters were monitored throughout the interventional procedure in the intensive unit care. None of the patients evaluated 30 days after TAVI died.

Statistical Analysis

The descriptive analysis was performed using SPSS statistics software (version 26 for Windows; SPSS Inc., Chicago, IL, USA). Continuous variables were reported as the mean ± SD and categorical ones as a number (frequency and percentages). The Kolmogorov–Smirnov test was used to assess the normal distribution of the data. Continuous variables were compared using the t-test (parametric analysis). Categorical variables were compared using Fisher's exact test.

Groups were compared using the $\chi 2$ or Fisher's exact test for categorical variables and ANOVA/ Student's t-test and Wilcoxon–Mann–Whitney U/Kruskal–Wallis tests for continuous variables, depending on their distribution. A p-value of ≤ 0.05 was considered statistically significant.

Ethics

The study was approved by the Ethics Committee of the University of Medicine and Pharmacy "Grigore T. Popa" Iași and of the Cardiovascular Diseases Institute Iași. All patients signed an informed consent statement, which mentioned that the results would be used for research purposes.

Results

We enrolled in our study 86 patients diagnosed with severe AS undergoing TAVI who have been assessed by a multidisciplinary team before and one month after the minimally invasive procedure.

Demographics, vital parameters, comorbidities and biological parameters at baseline and at 1-month follow-up are presented in Table 1. Predominantly female patients were included in our study (53.3%), with an average age of 75.8 ± 7.44 years old. In terms of anthropometric parameters, the mean value of BMI was equal both at enrollment and at progression (28.28 ± 3.19 kg/m^2 vs. 28.85 ± 2.66 kg/m^2) , not being a statistically significant parameter at one month after TAV($p = 0.054$). Two types of prostheses have been implanted, the most common being Edwards Lifesciences Sapien 3 (64 patients, 74.4%). The transfemoral approach was used in 83.7% of patients (72 cases). The average EUROSCORE score previously assessed by TAVI was 8.92 ± 10.60.

Patients with severe AS enrolled in our study had various comorbidities, the most significant being heart failure ($p < 0.001$), dyslipidemia (51.65%), concomitant coronary artery disease (48.84%), chronic kidney disease ($p = 0.042$) and hypertension (58.14%). 31.40% of our patients had diabetes mellitus. Of these, atrial fibrillation, heart failure and chronic kidney disease were also assessed prospectively, one month after TAVI. Thus, 81.4% of patients showed signs and symptoms suggestive of NYHA class II heart failure (70 patients), with the disappearance of severe NYHA class IV cases. In terms of chronic kidney disease, at one month after TAVI the percentage of patients with G3 involvement increased from 25.58%



to 32.56%. The main symptoms assessed in patients with severe AS were angina (73.3 vs. 34.9%, $p < 0.001$) or fatigue (9.3 vs. 47.7%, $p < 0.001$), both of which showed improvement secondary to interventional treatment. The one-month assessment also showed improvement in hemodynamic parameters, with improvements in systolic (149.07 ± 21.17 mmHg vs. 134.15 ± 11.21 mmHg, $p < 0.001$) and diastolic BP (82.72 ± 9.79 mmHg vs. 78.59 ± 8.64 mmHg, $p < 0.001$) (in the context of antihypertensive treatment administered), heart rate (73.35 ± 11.68 vs/ 68.09 ± 6.07, $p < 0.001$) and arterial oxygen saturation (89.76 ± 2.62% vs. 96.65 ± 1.59%, $p < 0.001$).

As part of the paraclinical assessment, both at enrolment and one month after TAVI, biochemical and hematological tests were collected. The mean hemoglobin value decreased peri-procedurally (12.54 ± 1.88 g/dl vs. 11.44 ± 1.86 g/dl, $p = 0.008$), similar to red blood cells (4.10 ± 0.79 mil. vs. 3.62 ± 0.75 mil, $p = 0.005$) and platelets (207069.77 ± 85475.94/mm^3 vs. 185093.02 ± 79127.84/mm^3, $p = 0.185$). On the other hand, the mean serum leukocyte value increased slightly (6930.81 ± 229.20/mm^3 vs. 7815.27 ± 2681.22/mm^3, $p = 0.018$), similar to inflammatory syndrome markers (with a $p < 0.001$ for fibrinogen and erythrocyte sedimentation rate <ESR>). Among the biochemical parameters special attention was attributed to renal function and lipid profile. Thus, the evaluation performed at one month showed a decrease in the mean serum values of total cholesterol (191.50 ± 56.21 mg/dl vs. 175.71 ± 43.88 mg/dl, $p < 0.001$) and LDL-cholesterol (135.38 ± 48.54 mg/dl vs. 123.07 ± 40.47 mg/dl, $p < 0.001$). The mean serum creatinine value showed a slight increase, without associated clinical significance (1.04 ± 0.35mg/dl vs. 1.10 ± 0.45 mg/dl, $p = 0.975$).

Discussion

We enrolled in our study a number of 86 patients with severe AS undergoing TAVI, and with the help of the evaluation performed one month after the minimally invasive procedure we demonstrated the beneficial effect of interventional treatment on clinical (angina <$p = 0.001$> and fatigue <$p < 0.001$>) parameters. In terms of demographic parameters, our study predominantly included female patients (53.3%), with a mean age of 75.8 ± 7.44 years old.

The role of age and gender of patients with severe AS in disease progression has been extensively studied in various clinical trials to date. There is a direct proportional relationship between the evolution of the clinical picture, the age of the patients and the periprocedural risk associated with TAVI, with older age correlating with a higher risk of

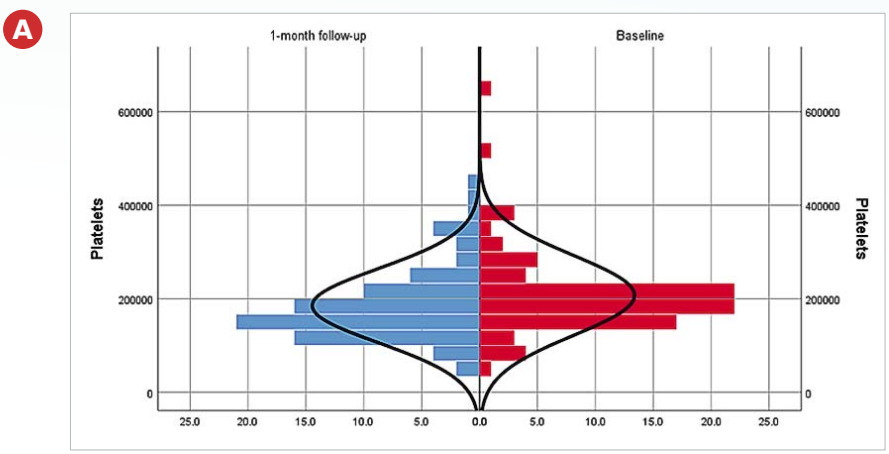
Parameters	Baseline	One Month Follow-Up	*p* Value
Age, y	75.8 ± 7.44		
Females	46 (53.3%)		
BMI, kg/m^2	28.28 ± 3.19	28.85 ± 2.66	0.054
Type of aortic prosthesis			
Edwards Lifesciences Sapien 3	64 (74.4%)		
Medtronic Evolut R	22 (25.6%)		
Vascular approach			
Transfemoral	72 (83.7%)		
Transapical	14 (16.3%)		
EUROSCORE II	8.92 ± 10.60		
Symptoms			
Angina pectoris	63 (73.3%)	30 (34.9%)	<0.001
Fatigue	83 (96.5%)	41 (47.7%)	<0.001
Comorbidities			
Atrial fibrillation	21 (24.4%)	22 (25.6%)	1
Heart failure	NYHA class III 62 (72.1%)	NYHA class II 70 (81.4%)	<0.001
	NYHA class IV 24 (27.9%)	NYHA class III 16 (18.6%)	
Dyslipidemia	47 (51.65%)		
Coronary artery disease	42 (48.84%)		
Peripheral artery disease	21 (24.42%)		
Stroke	7 (8.14%)		
COPD	14 (16.28%)		
Diabetes mellitus	27 (31.40%)		
Chronic kidney disease	G2 (53, 61.63%) G3 (22, 25.58%) G4 (2, 2.33%)	G2 (46, 53.49%) G3 (28, 32.56%) G4 (2, 2.33%)	0.042
Hepatopathy	20 (23.26%)		
Hypertension	50 (58.14%)		
Resting hemodynamics			
SBP, mmHg	149.07 ± 21.17	134.15 ± 11.21	<0.001
DBP, mmHg	82.72 ± 9.79	78.59 ± 8.64	<0.001
Heart rate, bpm	73.35 ± 11.68	68.09 ± 6.07	<0.001
Arterial oxygen saturation (%)	89.76 ± 2.62	96.65 ± 1.59	<0.001
Biological parameters			
Hemoglobin	12.54 ± 1.88	11.44 ± 1.86	0.008
Red blood cells	4.10 ± 0.79	3.62 ± 0.75	0.005
Leucocytes	6930.81 ± 229.20	7815.27 ± 2681.22	0.018
Fasting glucose	125.19 ± 46.56	115.67 ± 34.03	<0.001
Fibrinogen	481.69 ± 137.60	564.00 ± 204.61	<0.001
ESR	28.58 ± 24.13	31.66 ± 24.89	<0.001
Thrombocytes	207069.77 ± 85475.94	185093.02 ± 79127.84	0.185
Urea	53.50 ± 27.13	49.34 ± 26.12	0.014
Serum creatinine	1.04 ± 0.35	1.10 ± 0.45	0.975
eGFR, ml/min/1.73m^2	68.81 ± 18.11	66.81 ± 67.26	0.054
Total cholesterol	191.50 ± 56.21	175.71 ± 43.88	<0.001
LDL-cholesterol	135.38 ± 48.54	123.07 ± 40.47	<0.001
Triglycerides	114.24 ± 50.72	116.91 ± 44.51	0.649

Table 1. *Demographics, resting hemodynamics, comorbidities and biological findings at baseline and at 1-month follow-up. All values are expressed as mean ± standard deviation (SD) or n (%); y: years; BMI: body mass index; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; ESR: erythrocyte sedimentation rate; eGFR: estimated glomerular filtration rate; LDL-cholesterol: low-density lipoprotein cholesterol*

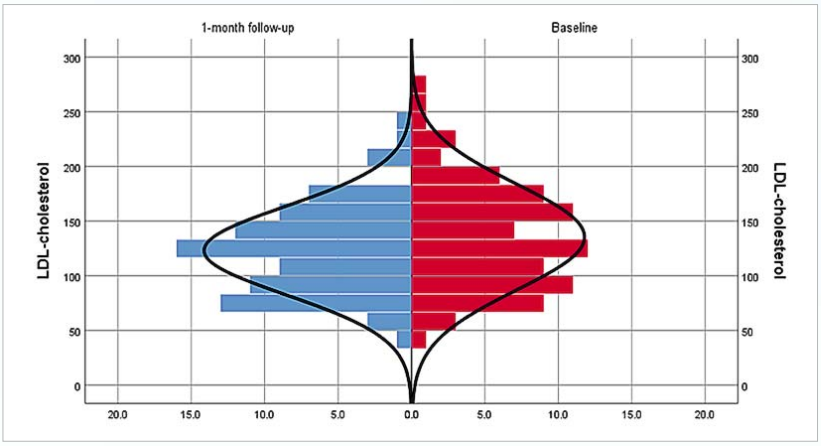
bleeding complications and therefore with a higher risk of post-procedural death especially in women[12-14]. Other clinical studies in the literature attribute additional risk to men through a higher risk of acute kidney injury or pacemaker implantation[15]. These aspects raise the observation of a greater concern regarding the medication (particularly the ones with a bradycardic effect), given the high risk of adverse effects or peri-procedural atrioventricular conduction disorders[16,17].

The evolution of technology has led to the manufacture of aortic valve prostheses with increasing performance and ease of use, resulting in the increasing use of TAVI as an alternative to traditional surgical replacement in selected patients[18-20]. In our study, the Edwards Lifesciences Sapien 3 prosthesis was used in 74.4% of patients, with results obtained at the one month after follow-up highlighting clinical improvement after TAVI. Beneficial results have also been reported in terms of short-term mortality risk, the Placement of Aortic Transcatheter Valves (PARTNER) trial showing a 20% reduction in the risk of death at one year and 18.3% at 2 years after TAVI[21,22]. Regarding the type of approach used, the statistical analysis carried out on our group of patients showed a preference for the transfemoral approach (83.7%).

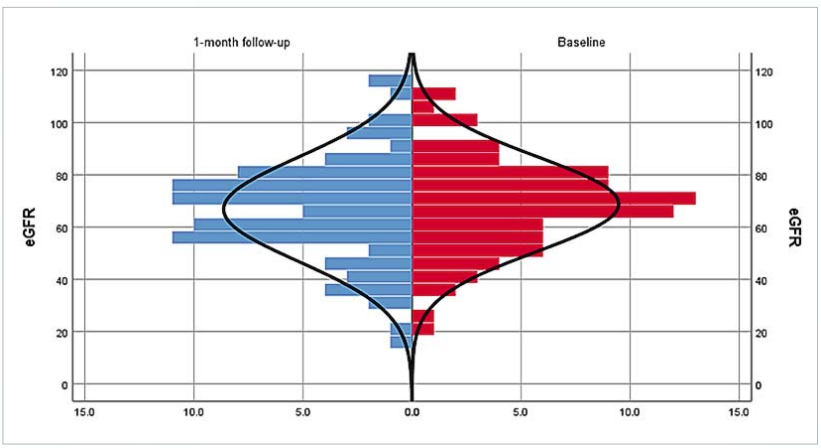
The efficacy of the two types of approaches has also been studied in the literature, with the apical approach being associated with a number of additional risks in terms of potential associated hemodynamic complications as well as the technique of



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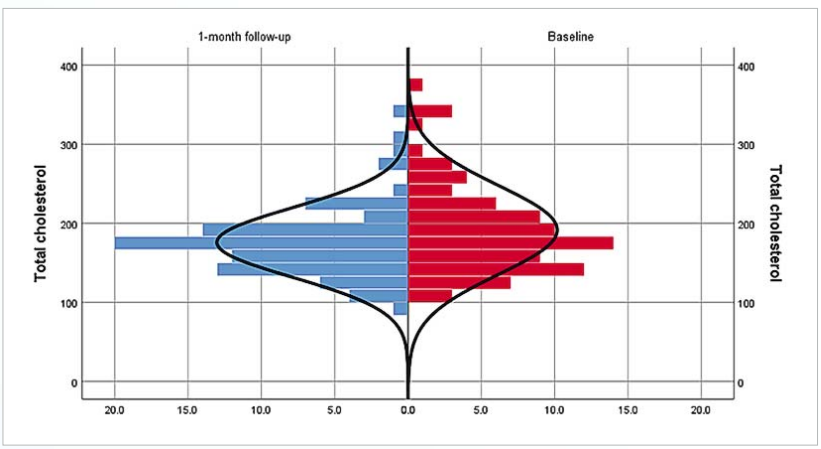


Figure 1. *Biological assessment at baseline and at the 1-month follow-up (eGFR: estimated glomerular filtration rate; LDL-cholesterol: low-density lipoprotein cholesterol)*



performing the approach requiring longer training[23,24].

TAVI is associated with a series of changes in functional parameters, predominantly echocardiographic, which indirectly modulate the improvement of symptoms in patients with severe AS undergoing this minimally invasive procedure. In our study we demonstrated the improvement of symptoms and New York Heart Association (NYHA) functional class of heart failure after one month so that the severe impairment specific to class IV NYHA disappeared and the percentage of patients with symptoms specific to class III NYHA decreased from 72.1 to 18.6% at the one-month follow-up (p <0.001). Statistical analysis also showed improvement in angina pectoris (p <0.001) and fatigue (p <0.001) in half of the patients enrolled in the study. The patients in our group were associated with multiple comorbidities that influence both peri-procedural risk and long-term outcome.

Dyslipidemia (51.65%), concomitant coronary artery disease (48.84%), chronic kidney disease (p = 0.042), diabetes mellitus and hypertension (58.14%) completed the clinical picture of a significant percentage of patients, justifying the need for ancillary multidisciplinary TAVI management with the aim of decreasing the risk of mortality. Clinical studies in the literature certify the role of associated pathologies in the assessment of prognosis, with special attention being paid not only to their presence but also to their number. Barth et al.[25] concluded that patients undergoing TAVI with less than 6 associated comorbidities have a halved risk of long-term death compared to patients with severe AS treated with drugs alone (p =0.004) which requires careful assessment for the choice of the optimal therapeutic decision.

Heart failure and chronic kidney disease require additional attention because of the complications they can induce and the impact on prognosis. Progression to heart failure requires an integrative approach, in which drug treatment and cardiovascular recovery complement the interventional therapeutic management of these patients[26-29]. Nilsson et al.[30] identified a number of predictors associated with a high risk of hospitalization or death after TAVI, the most significant being heart failure which accounts for 16% of hospitalizations from any cause and 50% from cardiovascular causes. Male gender, age over 90 years, association of atrial fibrillation, severe renal dysfunction, peripheral arterial disease and pulmonary hypertension are prognostic parameters identified by the same group of investigators.

In our study, polyvascular disease was present in a number of the patients enrolled in the study, the most common entities identified being peripheral arterial disease

(24.42%) and coronary artery disease (48.84%), with cerebrovascular disease being present in a small percentage of patients of only 8.14%.

In addition to comorbidities and demographic parameters, the statistical analysis also included biological parameters, assessed both at enrolment and one month after TAVI. In our study, serum hemoglobin (p =0.005) and platelet levels (p =0.0185) decreased one month after TAVI. The presence of anemia has been reported in 42-67%[31] of patients with severe AS undergoing TAVI, its persistence one year after the procedure being considered a negative predictor associated with increased mortality[32-35]. Also, persistence of anemia correlates with a high risk of rehospitalization in the first year after TAVI (odds ratio 1.91, p=0.024), while also influencing clinical status, by achieving reduced functional improvement and persistence of advanced-stage heart failure (odds ratio 0.49, p =0.034)[31].

The presence of anemia preoperatively is also associated with a negative prognosis both in the short term and in evolution, a meta-analysis published by Takagi et al.[36] et al. emphasizing the directly proportional relationship between decreased serum hemoglobin levels and increased risk of mortality in the short (p =0.003) and medium term (p <0.0001). Similar to anemia, thrombocytopenia is a common biological change in patients with severe AS undergoing TAVI. Khadija et al.[37] demonstrated that a reduction in platelet count of more than 30% is associated with a high risk of life-threatening bleeding, vascular complications or death within the first 30 days after the procedure.

In addition to hematological parameters, we also evaluated a series of biochemical data, with special attention to renal function and lipid profile. In our study, serum total cholesterol (p < 0.001) and LDL-cholesterol (p < 0.001) values decreased one month after TAVI, which is similar to clinical studies reported in some clinical trials in the literature. A group of investigators analyzed a cohort of 119 patients undergoing TAVI and demonstrated that low serum LDL-cholesterol and high density lipoprotein cholesterol levels independently correlated with a high risk of acute cardiac or cerebrovascular events in the short term[38].

Among the bio-humoral changes produced by TAVI are increased serum levels of inflammatory markers due to local injury. In a clinical study published by Khadija et al.[39] the duration of the procedure and the amount of contrast used correlates with an early inflammatory response in the first 24 hours after TAVI (p <0.01). In our study we demonstrated increased serum levels of leukocytes (p =0.018), fibrinogen (p <0.001) and ESR (p <0.001) compared to baseline levels, supporting the data presented in the literature.

Chronic kidney disease is frequently part of the clinical picture of AS patients undergoing TAVI, the serum creatinine level having both therapeutic and prognostic value[40]. Statistical analysis of biochemical data at one month showed a slight decline in renal function, similar to data presented in the literature to date. Older age, presence of comorbidities and use of an inadequate amount of contrast agents may lead to acute kidney injury after TAVI with a negative long-term prognostic role through the associated risk of progression to chronic kidney disease[41]. Most clinical studies attest to improved kidney function after TAVI, with visible results after only one month. Regular follow-ups has also shown a decreased risk of death after 2 years, while progression of renal



dysfunction has been associated with increased risk of morbidity and mortality[42].

Our study has several limitations due to the small number of cases analyzed and the subjective assessment of associated symptoms. We excluded cases where the clinical-paraclinical data were incomplete as well as those patients who did not present for follow-up one month after TAVI.

Conclusions

In conclusion, we demonstrated in our study that TAVI has a beneficial effect on both symptomatology and hemodynamic parameters. Biochemical changes identified one month after TAVI require dynamic evaluation to observe reversibility or transformation into predictors associated with a negative long-term prognosis.

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