

PERFORMANCE OF THE HEART TEAM APPROACH IN DAILY CLINICAL PRACTICE IN HIGH-RISK PATIENTS WITH AORTIC STENOSIS

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Abstract

Objectives: The Heart Team (HT) approach plays a key role in selecting the optimal treatment strategy for patients with aortic stenosis. Little is known about the HT decision process and its impact on outcomes. The aim of this study was to identify the factors associated with the HT decision, and evaluate clinical outcomes according to the treatment choice. **Methods:** The study included a total of 286 consecutive patients with aortic stenosis referred for discussion in the weekly HT meeting in a cardiovascular institute over 2 years. Patients were stratified according to the selected therapeutic approach: medical treatment (MT), surgical (SAVR) or transcatheter (TAVR) aortic valve replacement. Baseline characteristics involved in making a therapeutic choice were identified and a decision-making tree was built using CART methodology. **Results:** Based on HT discussion 53 patients were assigned to SAVR, 210 to TAVR and 23 to MT. Older patients (≥88-years-old) were mainly assigned to TAVR or MT according to the Logistic EuroSCORE (< or ≥28, respectively). While among younger patients (<88 years), significant mitral regurgitation (≥grade III), frailty, STS score and estimated glomerular filtration rate were the most relevant factors influencing treatment allocation. One-year all-cause mortality was 16.6% in the invasive groups (TAVR 17.2%, SAVR 14.0%) and 68.7% in the MT arm. **Conclusions:** The HT decision was determined by well-recognized risk factors which were used to define a treatment decision algorithm. Future studies with younger and lower risk patients may identify new contributory factors which may alter the selection process and treatment choice.

Introduction

Aortic stenosis (AS) is the most common valvular heart disease referred for valve replacement in developed countries. Since transcatheter aortic valve replacement (TAVR) emerged as an alternative treatment to surgery (SAVR) in moderate to high-risk patients with symptomatic severe AS, the Heart Team (HT) has developed a key role in patient selection and choice of therapeutic approach (1). In fact, decision making by a multidisciplinary HT is the recommended strategy according to both the European and American Guidelines (class I recommendation) (2,3).

The function of the HT should be to decipher complex clinical situations and recommend the most appropriate treatment based on currently available evidence and patient specific factors. A particularly complex clinical scenario, yet one commonly encountered in every day clinical practice, is the apparent lack of benefit in terms of post-procedural functional improvement or survival in a subgroup of patients undergoing TAVR

(4). In this setting, the HT theoretically can identify those patients in whom TAVR is likely to be futile. However, although team-based patient-specific decision making is generally accepted, very little information is available regarding the decision-making process, determinant factors of HT decisions, and outcomes of patients with AS discussed in the HT (5-7) . In order to improve patient selection and outcome and for a better understanding of the optimal care model, continuous evaluation of physician’s decisions are required. Therefore, the aims of this study were 1) to identify which factors influence the HT decision regarding the optimal therapeutic approach for a specific patient, and 2) evaluate patient’s clinical outcomes according to the assigned treatment.

Methods

The study prospectively evaluates consecutive patients with AS referred to the HT meeting between June 2014 and February 2017 collated in a dedicated database. Patients were referred from the catchment area of our main hospital and from two other satellite hospitals with an established alliance. Our study was approved by the Institutional Review Board of our institution and all patients provided written informed consent for the procedures. Heart team meetings were weekly scheduled in the main hospital with the attendance of at least two cardiac surgeons, two interventional cardiologists, one imaging cardiologist and one clinical cardiologist. Physicians from other specialities, such as internal medicine, oncology or geriatric medicine, were invited to participate in the discussion when necessary and physicians from the satellite hospitals participated fully via video-link. By closely following previous Clinical Practice Guidelines (2,3), a local consensus document (**Annex I in Supplementary data**) was developed and signed jointly by cardiac surgeons and cardiologists, with the aim of identifying potential candidates with AS for HT discussion. This document was distributed to all potential referral physicians within the three hospitals. All patients with AS originally referred for TAVR and those in whom the management was undecided were discussed by the HT and were included in this analysis. However, patients directly referred to SAVR who did not meet any of the criteria in the consensus document, were excluded from this analysis unless the cardiac surgeon deemed it necessary to discuss the case in the HT.

During the HT meeting, clinical data from each patient was summarized in a formal presentation, which also included a prospective evaluation of surgical risk using the logistic European System for Cardiac Operative Risk Evaluation logistic EuroSCORE and the Society of Thoracic Surgeons (STS) score. Each case presentation was followed by a discussion and assessment of the overall risk profile. The HT then decided to refer the patient to either medical treatment (MT), TAVR or SAVR. A prospective clinical follow-up at 1- 6- 12- and 24-month was carried out through clinical visits for all patients in the SAVR and TAVR groups, whereas clinical outcomes were analysed retrospectively in the MT group. The median follow-up time was 18 months [11-26] and only one patient was lost to follow-up. In-hospital and long-term outcomes were defined according to the Valve Academic Research Consortium 2 (VARC-2) criteria (8).

Quantitative continuous variables are expressed as mean (standard deviation) or median (interquartile range [IQR]) according to their distribution. Assessment of normality was performed using the Shapiro-Wilk test. Differences between treatment groups were evaluated using the non-parametric Kruskal-Wallis rank test and Wilcoxon rank test for continuous variables without normal distribution. Categorical variables were summarized as number (percentage) and comparisons were analysed by the chi-square or the Fisher’s exact test. Patient baseline characteristics were identified that significantly influenced decision making within the HT. Considering these factors, a decision tree to guide the decision-making process was built using CART (classification and regression tree) methodology (9). The CART method is used for constructing prediction models from data. The models are obtained by dividing the data and adjusting a simple prediction model within each partition. The programme determines cut-off points which best explain the categorical endpoint of the analysis (MT or TAVR or SAVR) and selects the predictor with the lowest p-value of a logistic regression to make a first division. The result is a decision tree. We used the registered baseline characteristics to reproduce the decision process by using the non-parametric CART methodology. Survival curves were calculated using the Kaplan-Meier method, and comparison was obtained with the log-rank test. All analyses were performed using Stata 14 (StataCorp, College Station, TX, USA) and RStudio Team

(2018). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA.

Results

A total of 286 consecutive patients with severe AS were included in the study. There was a progressive growth in the number of patients referred for HT discussion, with a 26% increase seen between the first and third time periods of the study. Of the 286 patients, 53 were referred for surgical therapy, 210 for TAVR (188 to transfemoral and 22 to non-transfemoral approach) and 23 were referred for MT (**Figure 1**). Reasons for choosing MT are summarized in **Table 1**.

Baseline characteristics according to the initial selected therapeutic strategy are shown in **Table 2**. Analysing data on an intention-to-treat basis, patients referred for SAVR were younger (82 [78-84] year-old) than patients in the TAVR and MT group (85 [81-87] and 86 [83-90] year-old, respectively) ($p < 0.001$). There were no significant differences in gender nor in cardiovascular risk factors. Patients in the SAVR group had lower risk scores than those assigned to TAVR or MT. Median left ventricular ejection fraction was lower in the MT group compared to TAVR and SAVR groups (55% [35-60] vs 60% [52-66] and 60% [51-64], respectively). Significant mitral regurgitation (MR[?]grade III) was less frequent in the TAVR group (5.5%) compared to MT and SAVR groups (42.1% and 22.0%, respectively, $p < 0.001$ for both comparison).

A total of 22 patients changed their therapy arm after being initially discussed in HT session due to various reasons (supplementary Table S1). Thus, considering the final definitive treatment, SAVR was performed in 50 patients, 195 patients underwent TAVR (176, 90.3% through transfemoral approach) and 41 patients received MT (**Figure 1**). Baseline characteristics according to definitive treatment group (as-treated group) are shown in **Supplementary Table S2**.

Fifteen baseline clinical characteristics were included in the CART analysis to determine relevant variables in the decision process (**supplementary Table S3**). Finally, the HT decision algorithm was built with six of those variables [age, logistic EuroSCORE, significant MR, frailty, STS score and estimated glomerular filtration rate (eGFR)] (**figure 2**). Age was the first split point identified with a cut-off value of 88 years old. Among patients 88-years and older, logistic EuroSCORE was the determinant parameter which assigned patients to TAVR or MT. Among patients <88 years old, significant MR was the next split variable. In patients with significant MR frailty was the conditioning variable to assign patients to SAVR or TAVR. In those without MR, STS score and eGFR were recognized as further relevant factors to decide between SAVR or TAVR.

Procedural characteristics and in-hospital outcomes among patients who underwent TAVR or SAVR are depicted in **Tables 3 and 4**, respectively. Importantly, 20% in the SAVR group underwent a concomitant second valve intervention. In-hospital mortality in the TAVR group was 4.6% and 12.0% in SAVR group. Specifically, in patients undergoing isolated aortic valve intervention in-hospital mortality was 7.5% with SAVR, compared with 3.4% in the transfemoral TAVR cohort ($p = 0.447$). While major vascular complications were more frequent in the TAVR group, acute kidney injury, significant bleeding, new onset atrial fibrillation and longer hospital stay occurred more frequently in the SAVR group. There were no differences between groups in terms of stroke or the need for permanent pacemaker implantation.

A total of 89 deaths were recorded during follow-up, 45 (53.6%) from a cardiac cause. In the as-treated analysis, all-cause and cardiovascular mortality at 1-year were 16.6% and 7.2% in the invasive groups (17.2% and 6.4% in the TAVR group, 14.0% and 10.2% in SAVR group), and 68.7% and 60.7% in the MT arm, respectively (**figure 3**). Survival rate according to access site (transfemoral versus non-transfemoral) and the type of surgery (single versus multiple valve intervention) are depicted in **figure 4**. The survival analysis according to the intention to treat are shown in **supplementary figure S1 and S2**. All cause rehospitalization rate and NYHA class in follow-up are shown in **supplementary figure S3**.

Discussion

The present study describes the HT treatment decision algorithm for a defined cohort of consecutive patients with severe AS from a tertiary referral hospital and two additional satellite hospitals. A local consensus

document was used to define the patients who needed to be discussed in the HT. After HT discussion, more than 50% of the patients were allocated to the TAVR group, and approximately 20% to each of the other treatment groups. Baseline characteristics that determined the allocation group were mainly older age, concomitant MR, surgical risk scores, renal function and frailty. Patients without intervention had a 1-year mortality rate which was three times higher than either of the intervention groups, mainly driven by cardiovascular death. Readmission rates at 1-year was close to 50% in both the TAVR and SAVR groups.

The HT concept stems from 2 randomized controlled trials comparing surgical and percutaneous strategies in coronary artery disease and AS (10,11). The purpose of the HT in these trials was to choose suitable candidates for both interventions. The function of contemporary HT discussions should be to apply the clinical acumen of the HT members to the selection of patients for medical, transcatheter and surgical treatment, as basing this decision purely on risk scoring systems may not properly reflect specific high-risk characteristics in some patients (12). As such, the HT approach provides a patient-specific decision based on the overall patient profile.

The role of the HT has become more prominent in recent years since the introduction of TAVR as an alternative treatment for severe AS, particularly in elderly patients with multiple comorbidities. The treatment of severe AS is a perpetually evolving area, with current evidence attesting to its value in lower risk patients (13,14), making continuous evaluation of HT decisions in this changing clinical environment of paramount importance. In our center, the HT format was designed by cardiac surgeons, and interventional, clinical and imaging cardiologists who take part in weekly meetings. Referral physicians also participated via video-link. The routine schedule of a weekly meeting dedicated entirely to patients with AS, allowed all resources to be focused on these patients to optimize the HT decision making process. The number of candidates referred to the HT increased over the years, suggesting a greater penetrance of the HT concept and, probably, greater value being placed in HT decisions by the referring physicians.

A critical aspect of the HT is to determine which patients would not benefit from an invasive approach and avoid futility (15). Reasons to avoid an invasive treatment were heterogeneous, but in general invasive treatment was avoided in patients considered to have a high-risk of mortality. The most common reasons to avoid invasive treatment were severe comorbidities or acute and critical illness. Despite careful decision making to avoid futile invasive procedures, a relatively high percentage of patients who underwent an invasive treatment died (~15%) or were readmitted (~40%) within one year, suggesting that the patient selection process could still be improved. Specially, patients referred to the TAVR group were very old and had several significant comorbidities, which conferred a high risk of dying from non-cardiovascular causes (more than half of the patients in this cohort). Continuous evaluation of the HT decisions, with a special focus on these high-risk patients, should be implemented to identify patients at higher risk of mortality and attempt to diminish future futile interventions. In our cohort HT decisions could be reconsidered if changes in the clinical situation arose and approximately 10% of the patients were subsequently changed from the initial allocated group.

Several factors (older age, significant MR, frailty, eGFR and surgical risk scores) defined by the CART analysis impacted the clinical decision making in accordance to others (6). Significant MR was identified as an important co-morbidity which increased the likelihood of referring the patient for surgery, particularly in those without frailty. However, the concomitant role of significant MR in patients with AS is still unresolved (16). Previous reports showed a negative impact of untreated baseline [?] grade III MR in both TAVR (17,18) and SAVR populations (19,20). On the other hand, a double valve intervention is associated to higher perioperative mortality than isolated SAVR (21). Among those with significant MR, frailty was a determinant factor to choose TAVR over SAVR. Frailty has been described as a strong predictor of peri-procedural complications and mid-term outcomes after cardiac surgery (22,23). However, in the setting of TAVR, frailty may not be significantly related to peri-procedural mortality or morbidity; although, it appears to have impact on mid-term outcomes (24). This may be due to the less physiologically stressful nature of TAVR compared to SAVR (25).

In our study, chronic kidney disease (CKD), a frequent comorbidity in patients with AS(26), increased the

chance of referring the patient for TAVR over SAVR. A previous study in patients with CKD has shown better short-term outcomes in TAVR compared to SAVR (27). Despite the well-recognized limitation of surgical risk scores in predicting outcomes in TAVR patients, systematic calculation of these scores provided useful and objective information for the HT discussion. Current European and American guidelines support their use for surgical risk stratification based on the inclusion criteria of randomized trials (2,3,28). Moreover, surgical scores still provide a general risk prediction in individualized patient and may predict a futile intervention (29).

The purpose of the study was not to compare different therapeutic options, due to the non-randomized nature of the interventions and the selection bias by the HT. However, general results were in accordance with previous registries and randomized trials with high-risk patients(11,28). While acute kidney injury, new onset atrial fibrillation and significant bleeding were higher in the SAVR group, vascular complications were more frequent in TAVR patients. Stroke and in-hospital mortality were similar. While residual aortic regurgitation tended to be higher in TAVR patients, valve hemodynamics overall were better in this group. Also, both invasive groups showed similar results in terms of long-term mortality and rehospitalization rates.

This study has the inherent limitations of any observational study without an external adjudication event committee. However, it demonstrates the practical real-world issues related to the current management of AS patients within a HT format. In this study we present the results of a single HT with a limited sample size. Additionally, not all patients with AS were evaluated by the HT. Although, wide-ranging criteria were prospectively set to define those that should be referred to the HT, a number of patients were treated without HT discussion and were not included in our study. Patients in the MT arm were not specifically followed-up and outcomes were identified in a retrospective fashion. This study spans the time period before the publication of trials on low risk patients, and the results cannot be extrapolated to current practice relating to patients in lower risk groups.

Figures Legends

Figure 1. Flow chart of patients referred to the Heart team.

Figure 2. Decision tree by CART analysis.

X|Y|W denote the number of patients allocated to each group: SAVR, TAVR and medical therapy, respectively. Ej. “2|6|0” indicate that 2 patients were assigned to SAVR, 6 to TAVR, and 0 to medical therapy.

Figure 3. Survival curve for all-cause (A) and cardiovascular (B) mortality according to treatment group.

Figure 4. Survival curve for all-cause (A) and cardiovascular (B) mortality in the intervention group according to TAVR approach and single versus multiple surgical valve intervention.

Table 1. Reasons for medical treatment decision.

Reasons for medical treatment decision	Initial decision n (23)	Final decision n (41)
Cardiac comorbidities: Severe left ventricular systolic dysfunction and/or severe mitral regurgitation.	5	5
Futility: Poor quality of life and/or cognitive impairment.	4	4
Acute illness.	4	7
Advanced cancer.	3	4
Patient /family refusal.	3	8

Reasons for medical treatment decision	Initial decision n (23)	Final decision n (41)
Death while awaiting complementary tests or while awaiting intervention.	2	9
Prohibitive surgical risk, unsuitable peripheral vasculature for TAVR.	1	1
Asymptomatic patient.	1	3

Table 2. Baseline characteristics in patients evaluated by the Heart Team according to allocated treatment: TAVR, SAVR or MT.

	MT (n=23)	TAVR (n=210)	SAVR (n=53)	Global p value	MT vs TAVR p value	MT vs SAVR p value	SAVR vs TAVR p value
Age, years	86 [83-90]	85 [81-87]	82 [78-84]	<0.001	0.087	<0.001	<0.001
Female sex	14 (60.9%)	116 (55.2%)	32 (60.4%)	0.727			
Body mass index, kg/m ²	25.9 [24.1-30.0]	27.0 [24.2-30.2]	28.0 [25.4-30.5]	0.321			
Diabetes mellitus	9 (40.9%)	76 (36.2%)	20 (37.7%)	0.899			
Hypertension	20 (90.9%)	183 (87.1%)	46 (86.8%)	0.871			
Coronary artery disease	14 (63.6%)	100 (47.6%)	21 (39.6%)	0.164			
Prior myocardial infarction	3 (13.6%)	33 (15.7%)	11 (20.8%)	0.630			
Prior CABG	2 (9.1%)	17 (8.1%)	4 (7.6%)	0.933			
Prior valvular surgery	1 (4.6%)	13 (6.3%)	7 (13.5%)	0.176			
Atrial fibrillation	12 (54.6%)	80 (38.1%)	21 (39.6%)	0.339			
Chronic obstructive pulmonary disease	3 (13.6%)	35 (16.7%)	7 (13.2%)	0.886			
Previous stroke	4 (18.2%)	31 (14.8%)	6 (11.3%)	0.675			
Peripheral vascular disease	1 (4.6%)	24 (11.4%)	3 (5.7%)	0.448			

	MT (n=23)	TAVR (n=210)	SAVR (n=53)	Global p value	MT vs TAVR p value	MT vs SAVR p value	SAVR vs TAVR p value
NYHA class III and IV	20 (90.9%)	155 (73.8%)	32 (60.4%)	0.020	0.076	0.009	0.054
Creatinine, mg/dL	1.1 [0.9-1.4]	1.0 [0.8-1.4]	1.0 [0.8-1.2]	0.659			
Dialysis eGFR (ml/min)	0 (0%) [53.5-66.6]	2 (1.0%) [62.8-81.3]	1 (1.9%) [63.3-81.9]	0.601			
Hemoglobin, g/dL	12.5 [10.8-13.6]	12.0 [10.8-13.1]	12.3 [10.7-13.4]	0.723			
Logistic EuroSCORE Frailty	18.4 [7.0-30.2]	13.7 [8.4-20.6]	10.0 [6.1-16.3]	0.017	0.327	0.032	0.009
STS score	18 (78.3%) [3.9-12.1]	104 (49.5%) [3.8-9.3]	12 (22.6%) [2.8-6.0]	<0.001	0.001	<0.001	<0.001
	5.6 [3.9-12.1]	5.4 [3.8-9.3]	3.8 [2.8-6.0]	0.002	0.713	0.038	<0.001
Echocardiographic Variables	Echocardiographic Variables	Echocardiographic Variables	Echocardiographic Variables	Echocardiographic Variables	Echocardiographic Variables	Echocardiographic Variables	Echocardiographic Variables
Left ventricular ejection fraction, %	55 [35-60]	60 [52-66]	60 [51-64]	0.017	0.005	0.027	0.477
LVEF < 37.5%	5 (26.3%)	17 (8.1%)	6 (11.3%)	0.041	0.010	0.464	0.119
Maximum aortic gradient, mmHg	62 [41.5-73]	75 [62-90]	77.6 [65-90]	0.061			
Mean aortic gradient, mmHg	36.0 [24.0-48.5]	43.2 [38.0-56.0]	45.0 [41.0-54.2]	0.073			
Aortic valve area, cm ²	0.8 [0.5-0.9]	0.6 [0.5-0.8]	0.7 [0.5-0.8]	0.101			
Grade III and IV Mitral regurgitation	8 (42.1%)	11 (5.5%)	11 (22.0%)	<0.001	<0.001	0.095	<0.001
Pulmonary hypertension	6 (33.3%)	69 (33.2%)	13 (25.5%)	0.566			
PASP, mmHg	34 [20-50]	20 [20-45]	39 [20-54]	0.046	0.032	0.207	0.166

Values are expressed as median [IQR] or n (%). eGFR: estimated glomerular filtration rate, MT: medical treatment, NYHA: New York Heart Association, PASP: pulmonary artery systolic pressure, STS: Society of

Table 3. Procedural details according to treatment group: TAVR or SAVR

	TAVR (n=195)	SAVR (n=50)	p value
Prosthesis type	Prosthesis type	Prosthesis type	Prosthesis type
SAPIEN XT. Edwards	37 (19.0%)		N/A
SAPIEN 3. Edwards	94 (48.2%)		
CoreValve. Medtronic	8 (4.1%)		
Evolut R. Medtronic	41 (21.0%)		
Portico. St Jude Medical	6 (3.1%)		
Symetis. Boston Scientific	6 (3.1%)		
Other THV	2 (1.0%)		
Trifecta St Jude Medical		18 (36.0%)	
Mitroflow. Sorin		11 (22.0%)	
Perimount Magna Ease. Carpentier-Edwards		9 (18.0%)	
Intuity. Edwards		7 (14.0%)	
Other surgical valves		5 (10.0%)	
Prosthesis size	Prosthesis size	Prosthesis size	Prosthesis size
19-23 mm	71 (37.0%)	44 (88.0%)	<0.001
25-27 mm	74 (38.5%)	4 (5.1%)	
29-31 mm	47 (24.5%)	2 (4.0%)	
Transfemoral approach	176 (90.3%)	N/A	N/A
Surgical procedures	Surgical procedures	Surgical procedures	Surgical procedures
SAVR +/- CABG		40 (80%)	
SAVR + mitral valve surgery +/- CABG		3 (6%)	
SAVR + tricuspid valve surgery +/- CABG		3 (6%)	
SAVR + mitral and tricuspid valve surgery		2 (4%)	
SAVR + other procedures		2 (4%)	

Values are expressed as median [IQR] or n (%). CABG: coronary artery bypass grafting, SAVR: surgical aortic valve replacement, THV: transcatheter heart valve.

Table 4. In-hospital complications according to treatment group: TAVR or SAVR

	TAVR (n=195)	SAVR (n=50)	p value
Clinical endpoints	Clinical endpoints	Clinical endpoints	Clinical endpoints
In-hospital mortality	9 (4.6%)	6 (12.0%)	0.053
In-hospital mortality (TF-TAVR versus isolated surgical aortic valve intervention)	6/176 (3.4%)	3/40 (7.5%)	0.447
Stroke	3 (1.6%)	2 (4.0%)	0.272

	TAVR (n=195)	SAVR (n=50)	p value
Major vascular complication	15 (7.9%)	0 (0%)	0.046
Bleeding complications	Bleeding complications	Bleeding complications	Bleeding complications
Life-threatening	12 (6.2%)	6 (12.0%)	0.161
Major	13 (6.7%)	14 (28.0%)	<0.001
Life-threatening or major	25 (12.9%)	20 (40.0%)	<0.001
Acute kidney injury	Acute kidney injury	Acute kidney injury	Acute kidney injury
Stage 1	29 (15.0%)	15 (30.0%)	0.014
Stage 2 or 3	7 (3.6%)	9 (18.0%)	<0.001
Any stage	36 (18.7%)	24 (48.0%)	<0.001
New permanent pacemaker implantation	27 (13.9%)	6 (12.0%)	0.724
New onset atrial fibrillation	14 (7.3%)	15 (34.9%)	<0.001
Length of ICU stay, days	1 [1-2]	3 [1-7]	<0.001
Length of hospital stay, days	7 [5-10]	9 [6-16]	0.005
Echocardiographic endpoints	Echocardiographic endpoints	Echocardiographic endpoints	Echocardiographic endpoints
Aortic regurgitation [?] ²	20 (10.9%)	1 (2.6%)	0.137
Aortic regurgitation [?] ³	10 (5.5%)	0 (0%)	0.217
Mean aortic gradient, mmHg	8.6 [6.1-12.0]	12.0 [8.0-14.0]	0.007

Values are expressed as median [IQR] or n (%). ICU: intensive care unit, TF-TAVR: transfemoral – transcatheter aortic valve replacement.

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