REVIEW TOPIC OF THE WEEK

Aortic Stenosis and Perioperative Risk With Noncardiac Surgery



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ABSTRACT

Aortic stenosis (AS) is characterized as a high-risk index for cardiac complications during noncardiac surgery. The American College of Cardiology/American Heart Association guidelines define severe AS as aortic valve area ≤ 1 cm², mean gradient of ≥ 40 mm Hg, and peak velocity of ≥ 4 m/s. As per current clinical practice, any of these characteristic features label a patient as at high risk for noncardiac surgery. However, these parameters appear inconsistent, particularly with respect to the aortic valve area cutoff value. The perioperative risk associated with AS during noncardiac surgery depends upon its severity (moderate vs. severe), clinical status, and the complexity of the surgical procedure (low to intermediate risk vs. high risk). A critical analysis of old and new data from published studies indicates that the significance of the presence of AS in patients undergoing noncardiac surgery is overemphasized in studies that predate the more recent advances in echocardiography and cardiac catheterization in assessment of aortic stenosis, anesthetic and surgical techniques, as well as post-operative patient care. (J Am Coll Cardiol 2015;65:295-302) © 2015 by the American College of Cardiology Foundation.

75-year-old Caucasian male presents to the clinic with the chief complaint of bilateral buttock and thigh pain. During clinical examination, a heart murmur is appreciated. He is otherwise asymptomatic. He undergoes lower leg arterial and carotid duplex examinations, which show moderate arterial insufficiency of both legs and 70% to 99% stenosis of the left common carotid artery with an internal carotid artery/common carotid artery ratio of 4.14. The echocardiogram report notes severe aortic stenosis (AS) with aortic valve area (AVA) 0.73 cm². The peak velocity is 3.5 m/s, the peak gradient is 46 mm Hg, the mean gradient is 25 mm Hg, and the ejection fraction (EF) is 50% to 55% (visually assessed), with cardiac output (CO) 4.3 l/min. He is referred for aortic valve replacement (AVR).

During workup, he is found to have a porcelain gall bladder. Transesophageal echocardiography (TEE) reports AVA by planimetry of 0.81 cm² and by continuity equation of 0.91 cm², mild mitral regurgitation (MR), and aortic regurgitation. TEE also shows a mobile complex atheromatous plaque, measuring 2.5×0.72 cm², at the junction of the aortic arch and descending aorta. Cardiothoracic surgeons deem this patient to be at "prohibitive risk" for AVR. Planned carotid endarterectomy and laparoscopic cholecystectomy are also subsequently cancelled due to the high risk associated with "severe aortic stenosis."

Many clinicians with patients 65 years or older face the type of clinical conundrum described in the preceding text. AS affects approximately 2% to 9% of this population (1-3), who also regularly require noncardiac surgical procedures for other comorbidities. After Skinner and Pearce (4) first noted a high rate of cardiovascular complications and death in "patients with aortic lesions," Goldman et al. (5) and Detsky et al. (6) characterized AS as a high-risk index for cardiac complications during noncardiac surgery. Over the years,



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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area EF = ejection fraction

MI = myocardial infarction

TAVR = transcatheter aortic valve replacement

many similar reports have emerged (4-8) (**Table 1**), re-emphasizing the perioperative risk associated with "aortic stenosis" during noncardiac surgery. Unfortunately, these conclusions have been on the basis of limited details and ambiguous definitions of AS severity.

In the midst of all this, a prospective clinical trial to validate the Cardiac Risk Index (9)

noted no significant correlation between "critical aortic stenosis" and perioperative complications during noncardiac procedure. This has been largely ignored, perhaps due to a very small sample size of only 5 patients, representing 0.21% of the total patients with AS. The established paradigm has invariably led to either patient ineligibility for an essential surgical surgery or referral for AVR, even in asymptomatic patients with AS of varying severities. For these patients with AS to have required noncardiac surgeries, they are subjected to a <u>6% to</u> 13% perioperative risk during AVR (10) and an at least 1% risk of prosthetic-related complications per year (11).

What is even more troubling is that many times, patients undergo aortic valvotomy with dubious results (residual stenosis in the moderate to severe range, mostly AVA 1 cm²) and unacceptable rates of periprocedural complications, including death (12). This is despite the statement in the 2006 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (13) that, "most asymptomatic patients with severe aortic stenosis can undergo urgent noncardiac surgery at a reasonably low risk." and balloon valvotomy is not recommended.

In contrast, the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery (14) recommended percutaneous balloon valvuloplasty as a "bridge to surgery" in hemodynamically unstable patients who could not undergo AVR. The 2007 guidelines also labeled severe AS as "the greatest risk for noncardiac surgery," and quoted a 10% mortality risk for patients with AS. The current 2014 ACC/AHA guidelines (15) on valvular heart disease recommend moderate-risk, elective noncardiac surgery in patients with asymptomatic severe AS (Class IIa, Level of Evidence: B). However, they also state that, "in patients with moderate to severe aortic stenosis, the 30-day mortality is higher for patients with aortic stenosis (2.1%) compared with propensity score matched controls (1%) with higher risk of post-operative MI" (15), a statement shared by the 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery (16).

The basis for all of these statements are published reports that included a cohort of AS patients who were symptomatic, had left ventricular systolic dysfunction/congestive heart failure, or had concomitant significant other valvular pathology, in particular, MR (Table 2) (17-23). Those reports do not truly represent patients with "asymptomatic severe aortic stenosis," as described earlier in this review.

Calleja et al. (22) is the only analysis to exclude "<mark>symptomatic</mark> aortic stenosis" and to report similar rates of myocardial infarction (MI) or death during noncardiac surgery in asymptomatic patients with severe AS compared with control subjects. Even the report from Agarwal et al. (17), which was widely quoted in the 2014 ACC/AHA guidelines, did not show any significant differences in composite outcomes (30-day mortality or post-operative MI) between patients with asymptomatic severe AS (4.7%) versus control subjects without AS (2.7%). A recently published report by Tashiro et al. from the Mayo Clinic (23) shows identical rates of death and MACE (major adverse cardiovascular events) for asymptomatic patients with AS and controls without AS (30-day mortality 3.3% vs. 2.7% and MACE 12% vs. 12%). Table 3 summarizes the outcomes of intermediate-risk to high-risk (including vascular) surgery in patients with asymptomatic severe AS versus controls without AS, matched using the Revised Cardiac Risk Index.

In the reports from both Agarwal et al. (17) and Tashiro et al. (23), primary adverse outcomes are significantly higher in AS patients with typical symptoms of angina, syncope or dyspnea; low left ventricular EF; or other concomitant significant valvular disease, particularly MR or tricuspid regurgitation. This trend holds, irrespective of the severity of AS, as in the report of Agarwal et al. (17), where even patients with moderate AS experienced adverse cardiovascular events if they had EF <40% (present in 35.3% patients) and moderate to severe MR (present in 29.4% patients).

Even more perplexing is the ACC/AHA-recommended grading of AS severity. In current clinical practice, echocardiography has become the main/ only tool for grading the severity of AS. Echocardiography may generally underestimate velocities and gradients. However, particularly in the older population, it usually <u>underestimates</u> left ventricular outflow tract <u>diameter</u> due to <u>calcification</u>, basal septal hypertrophy, and outflow tract narrowing. Left ventricular outflow tract <u>diameter</u>, which is <u>squared</u> in the continuity equation, leads to <u>overestimation</u> of the <u>severity</u> of <u>AS</u> on basis of the AVA estimation.

Finding any of the 3 parameters for severe AS, as recommended by the ACC/AHA (AVA $\leq 1 \text{ cm}^2$, peak

TABLE 1 Studies Showing High Perioperative Risk in Patients With AS Undergoing Noncardiac Surgery						
First Author, Year (Ref. #)	Number of Patients (AS/Total)	Severity of AS	Cardiac Complications			
Skinner and Pearce, 1964 (4), retrospective	59/766	Not specified "Patients with aortic lesion"	10% mortality			
Goldman et al., 1977 (5)	23/1,001	"Probable important aortic stenosis" on the basis of clinical examination, cardiac catheterization in some	13% cardiac death; 17.3% cardiac complication;4% nonfatal complications			
Detsky et al., 1986 (6), prospective	20/455	"Suspected critical stenosis with a 50 mm gradient" on the basis of clinical examination and ECG	Not specified			
Rohde et al., 2001 (7)	67/570	Peak instantaneous aortic gradient of \ge 40 mm Hg	Cardiac complications OR: 6.8, 95% CI: 1.3-3.1			
Zahid et al., 2005 (8), retrospective	5,149/10,284	Aortic stenosis identified by ICD-9 code from national hospital discharge records Case-control grading of severity of AS not known	55% greater risk of MI, but no increased mortality			

AS = aortic stenosis; CI = confidence interval; ECG = electrocardiography; ICD-9 = International Classification of Diseases-9th Revision; MI = myocardial infarction; OR = odds ratio.

<u>velocity >4 m/s</u> or a mean <u>gradient ≥40 mm Hg</u> on echocardiography), results in AS being graded as severe, and labels the patient at high risk for noncardiac surgery. The <u>problem</u> with this grading is the <u>discrepancy</u> between the <u>degrees</u> of AS <u>severity</u> on the <u>basis</u> of these <u>parameters</u>. A 4-m/s peak velocity may not correspond to a mean gradient of ≥40 mm Hg, and should give an AVA of 0.81 to 0.82 cm² using the Gorlin formula. Moreover, an AVA of 1 cm² will correspond to a peak velocity of 3.1 m/s, and a mean gradient of 40 mm Hg should correspond to an AVA of 0.75 cm².

Minners et al. (24) clearly showed this discrepancy with 3,483 echocardiography studies. They found that 30% of patients with severe AS by AVA had nonsevere stenosis by mean gradient and that 25% had nonsevere stenosis by peak velocity. Correction of AVA for body surface area <0.6 cm²/m² did not markedly change the results with respect to the comparison of AVA and mean gradient. More than 39% of patients with a body surface area-adjusted AVA \leq 0.6 cm²/m² had a mean gradient <40 mm Hg. Only 6% of patients diagnosed with severe aortic stenosis on the basis of peak velocity had a mean gradient of 40 mm Hg.

Echocardiography estimates the effective orifice area (EOA), which is always smaller by a variable coefficient of contraction than the actual anatomical area measured at catheterization using Gorlin's formula. Depending on the morphology of stenosis and rheological characteristics of the blood, the coefficient of contraction varies by almost 29% (25,26). Thus, for a given anatomical orifice, the EOA may be smaller by a factor of one-third.

Using the Medtronic aortic bioprosthesis and left heart pulse duplicator system (Medtronic, Minneapolis, Minnesota), Dumesnil et al. (27) showed that Gorlin's formula yields 1% to 2% higher AVA than the continuity equation.

A physiologically unsafe parameter of AS that is not causing symptoms, but will cause perioperative complications during a noncardiac surgery, has never been defined. The current ACC/AHA-recommended parameters for severe AS were adopted after they

TABLE 2 Studies Showing High Perioperative Risk in Patients With Aortic Stenosis During Noncardiac Surgery								
First Author (Ref. #)	Classical AS Symptoms Angina, Syncope, Dyspnea	Heart Failure EF <55%; History of CHF	Other Valvular Disease					
Raymer et al. (18)	45% patients with angina	NA; 38%	Not reported					
Torsher et al. (19)	84% patients with at least 1 and 16% with 2 classical symptoms	25% (16/19); NA Range 30%-85%	12 mild MR, 9 mild AR, 4 moderate AR					
Rohde et al. (7)	Not reported	25% with mild to severe systolic dysfunction	NA					
Kertai et al. (20)	20% with 1 or more classical symptoms: 24% angina	54% patients with EF ${<}35\%{-}49\%$	24% with other valvular disease: MR 7%, TR 7%, AR 10%, MS 6%					
O'Keefe Jr. et al. (21)	75% with classical symptoms: angina 40%, syncope 15%, dyspnea 50%	66% with CHF	NA					
Agarwal et al. (17)	29.5% with classical symptoms	Only EF <40% was reported in 7%; history of CHF 13%	Severe MR 4%					
Tashiro et al. (23)	41.4% symptomatic: angina 9.4%, syncope 3.9%, dyspnea 36.6%	18.4% with heart failure	MR 15.5%, TR 16.7%, MS 4%					

AR = aortic regurgitation; AS = aortic stenosis; CHF = congestive heart failure; EF = ejection fraction; MR = mitral regurgitation; MS = mitral stenosis; NA = not available; TR = tricuspid regurgitation.

	Co	omposite Out	come	30-Day Mortality			Post-Operative MI			Intraoperative Hypotension		
First Author (Ref. #)	AS	Control	p Value	AS	Control	p Value	AS	Control	p Value	AS	Control	p Value
Calleja et al. (22)	3.3	3.3	NS	0	1.6	0.93	3.3	3.3	0.74	30	17	0.11
Agarwal et al. (17)	4.7	2.7	0.2	1.2	1.3	0.90	3.5	1.4	0.06	Not rep	oorted	
Tashiro et al. (23)	12.0	12.0	1.0	3.3	2.7	0.73	1.3	1.9	NS	25.3	17.6	NS

were shown to predict development of symptoms or a requirement for valve replacement in patients with AS within 2 to 5 years (28,29).

This raises the question of which echocardiographyderived parameter(s) of AS should label a patient as high risk for noncardiac surgery. Clinical experience with Gorlin's formula-based valve area calculation at catheterization led to the concept that symptoms develop when the area falls below 0.8 to 0.9 cm² in AS. The European Society of Cardiology guidelines state that, "severe aortic stenosis is unlikely if cardiac output is normal and there is a mean gradient <50 mm Hg" (30).

Analysis of the available data from published reports indicates that on the basis of echocardiography, adverse events during noncardiac surgery occurred primarily in patients with an AVA ≤ 0.7 cm² and a mean gradient ≥ 50 mm Hg (Table 4) (31). The only report (17) to show adverse outcomes in patients with a lower AVA or mean gradient (as low as 15.0 \pm 6.5 mm Hg) also stipulated that LV systolic dysfunction and MR are serious confounding factors. This is understandable because, despite a large pressure overload, oxygen consumption may be normal, or

even low, in AS (chronic pressure load) as long as heart size and systolic wall stress are normal. Even a small left ventricular cavity enlargement or decrease in systolic function from any cause can substantially increase the likelihood of decompensation under stress, thereby leading to complications during noncardiac surgery. The ventricular workload and oxygen consumption also depend upon the compliance of the valve. A failure to increase the size of the EOA during stress leads to a greater increase in workload and systolic wall stress. Compliance was reportedly low in symptomatic patients with AS (32).

If the preceding data are to be believed, then asymptomatic patients with AS with an AVA >0.8 cm², mean gradient <45 to 50 mm Hg, and preserved LV systolic function should not be labeled as high risk for a noncardiac surgery. Their perioperative cardiac risk should be assessed by revised cardiac risk index only, as shown by Lee et al. (9).

The adverse outcomes feared during noncardiac surgery in patients with AS are mostly attributable to the anesthetic and surgical stress. The fixed aortic valve obstruction impedes an appropriate hemodynamic response during anesthesia and stress.

TABLE 4 Relationship of Valve Area and Mean Gradient to Post-Operative Complications During Noncardiac Surgery in Patients With AS						
First Author (Ref. #)	AVA	Mean Gradient, mm Hg	Remarks			
Detsky et al. (6)	Not reported	Gradient 50	Gradient mean or peak?			
Raymer et al. (18)	Mean 0.9 cm ²	Not reported	Death in patient AVA 0.7 cm ²			
Torsher et al. (19)	$0.67\pm0.10~\text{cm}^2$	55 ± 15	2 deaths: AVA 0.6 cm ² Mean gradient 49 mm Hg AVA 0.7 cm ² Mean gradient 58 mm Hg			
Kertai et al. (20)	Mean 0.6 \pm 0.1 cm^2	31% complication rate with mean gradient >50; 11% complication rate with mean gradient 25-49				
Leibowitz et al. (31)	$0.71\pm0.17~\text{cm}^2$	38.2 ± 12.0				
Calleja et al. (22)	0.8 cm ²	50				
Agarwal et al. (17)	Severe AS <1.0 cm ² , Moderate AS 1.0-1.5 cm ²	$\begin{array}{l} 48.6 \pm 12.3 \\ 15.0 \pm 6.5 \end{array}$	2 patients had MR 35% with EF ${<}40\%$, 29.4%			
Tashiro et al. (23)	Mean 0.9 \pm 0.2 cm^2	40 \pm 11 mm Hg	Mortality 7.4% in AS V/S, 5.9% in control with mortality 9.8%, AS V/S 2.4% when mean gradient >50 mm Hg			
AVA = aortic valve area; V/S = very severe/severe; other abbreviations as in Table 2.						



This figure demonstrates the clinical conundrum faced by clinicians in the evaluation of noncardiac surgical risk assessment in patients with aortic stenosis based on current guidelines. The **final column on the right** illustrates potential considerations in evaluating these difficult patients. ACC/AHA = American College of Cardiology/American Heart Association; AS = aortic stenosis; AVA = aortic valve area; EOA = effective orifice area; LVOT = left ventricular outflow tract; MI = myocardial infarction.

Chronic pressure overload-induced concentric hypertrophy, low myocardial compliance with pre-loaddependent cardiac output, and low coronary reserve with or without coronary obstruction all contribute to this insufficiency.

A fall in vascular resistance during anesthesia results in hypotension because of inadequate compensatory increase in cardiac output due to fixed obstruction. Hypotension, in turn, reduces coronary perfusion, leading to myocardial ischemia and a downward spiral of reduced contractility. This causes a further fall in blood pressure and coronary perfusion, ultimately leading to MI and death. Volatile or intravenous general anesthesia tends to reduce sinus node automaticity and may lead to nodal rhythm, other arrhythmias, and myocardial depression. Tachycardia and loss of atrioventricular synchrony due to volatile anesthetic agents or arrhythmias (e.g., atrial fibrillation or atrial tachycardia) subsequently compromise the atrial contribution to ventricular filling. This leads to heart failure and hypotension. The presence of any other significant valvular lesion, in particular MR or left ventricular systolic dysfunction, further adds to the complexity and makes perioperative management during noncardiac surgery difficult.

Compared with historical reports, the cardiac risk during noncardiac surgery in patients with aortic stenosis appears to have significantly declined in recent times due to increased awareness of hemodynamic concerns and recent advances in anesthetic and surgical approaches. This conclusion is exemplified by the 30-day mortality rates of 2.1% and <5% reported in 2 large, recently published reports (17,23) in patients with AS during elective noncardiac surgery, comparable to the expected 1% to 5% mortality in intermediate-risk surgery and >5% in high-risk surgery in patients without AS mentioned in the ACC/AHA guidelines (14). Understandably, mortality was higher (5.9%) when emergent/urgent noncardiac surgical procedures were included (23). A review of published reports that included anesthetic and intraoperative details revealed that, in these patients, noncardiac surgeries were mostly performed using balanced or general anesthesia. No intraoperative deaths were reported. The most commonly reported intraoperative event was the occurrence of hypotension requiring vasopressors, which varied in incidence, ranging from 15% (22) to 30% (17) to 74% (20) in different reports. Hypotension was aggressively and successfully treated, preferably with phenylephrine, in most instances. Phenylephrine was the preferred vasopressor agent for treatment of hypotension in these patients, perhaps because it is well tolerated in patients with AS without impairment of left ventricular global function. The ventricular afterload in these patients mainly depends on the pressure gradient across the aortic valve, rather than on systemic vascular resistance (33). Phenylephrine increases coronary perfusion pressure without significant chronotropic side effects, and it also improves left ventricular filling dynamics, possibly by increasing left atrial pressure (34).

On 1 occasion, insertion of a temporary pacemaker was required without any further adverse incidents (20). Use of central neuraxial blocks (epidural/spinal) was mentioned in some earlier reports, but not in more recent reports. Their use was, perhaps, avoided due to their potential to excessively decrease systemic vascular resistance and hypotension.

In most reports, the anesthesia time and duration of surgery were longer in patients with AS compared with control subjects. Classic tenets of intraoperative anesthetic management in these patients include: avoiding decrease in pre-load; adequate volume loading; maintaining high-normal systemic vascular resistance and contractility; preventing prolonged tachycardia; and maintenance of sinus rhythm. These tenets, along with close intraoperative monitoring with the help of an arterial line and right heart catheter, and post-operative monitoring in intensive care units for at least 24 to 48 h appears to have improved the safety of noncardiac surgeries in these patients.

In **some** centers, **TEE** is used additionally to monitor cardiac chamber sizes intraoperatively.

In the report by Tashiro et al. (23), the presence of atrial fibrillation was associated with higher mortality in patients with severe AS undergoing noncardiac surgery on both univariate and multivariate analysis. In that report, 18.4% of patients with severe AS had atrial fibrillation, with a higher incidence (24.5%) in symptomatic patients versus asymptomatic patients (14%).

Earlier, atrial fibrillation was reported in 9.1% of patients with mild to moderate AS in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study (35). Atrial fibrillation was reported in 10% of patients from a 397-patient cohort, of whom 87.3% had severe AS (AVA <1.2 cm² by the Gorlin formula) (36). In this report, atrial fibrillation tended to be associated with less severe AS, lower cardiac output, lower peak gradient, and higher pulse pressure.

Indeed, due to loss of the atrial contribution to ventricular filling and loss of atrioventricular synchrony, patients with AS poorly tolerate atrial fibrillation, and tend to develop symptoms at the onset of the arrhythmia. The presence of atrial fibrillation was reported to increase 30-day post-operative mortality (6.4%), even in patients without AS undergoing noncardiac surgery (37). Thus, the increased mortality in Tashiro et al. (23) is not surprising. The presence of atrial fibrillation in asymptomatic patients with AS raises questions regarding their symptom status and may point toward other associated valvular diseases, in particular mitral valve disease, left ventricular systolic dysfunction, and/ or pulmonary hypertension from any cause.

There is not much published data on the group of patients with paradoxical low-flow, low-gradient AS with preserved LV systolic function. Tashiro et al. (23) found that 10 of these patients (3.8% of the total) did not show any additional risk of perioperative complications.

Selection bias in the published reports cannot be entirely ruled out, as these were all retrospective studies and may not have included high-risk, severe AS patients who were either referred for AVR or did not undergo the necessary noncardiac surgery. However, most reports used currently recommended methods and parameters to grade the severity of AS and have well-matched control subjects, making them credible and representative of patients seen in day-to-day practice. The **Central Illustration** shows the current clinical conundrum and illustrates potential considerations during evaluation of these difficult patients with aortic stenosis for noncardiac surgery.

One option for risk stratification in these patients may be assessment by echocardiography of increases in valve gradients during exercise, which may reflect high stiffness and low compliance of the valve, indicating high likelihood of hemodynamic compromise under anesthesia for noncardiac surgery. A \geq 18 mm Hg increase in the mean gradient during exercise predicts increased cardiac events during follow-up in asymptomatic, severe AS (38). In view of the association of coronary artery disease with aortic stenosis, the safety of these patients, at least before intermediate- to high-risk noncardiac procedures, should be increased by excluding hemodynamically significant coronary artery disease, preferably by coronary angiography.

Recently, transcatheter aortic valve replacement (TAVR) has emerged as a viable option for high-risk patients with symptomatic aortic stenosis who cannot undergo surgical AVR. However, there are currently no data for the efficacy of TAVR in patients with AS undergoing noncardiac surgery. Moreover, reported periprocedural and 30-day TAVR outcomes (mortality 7.8%; stroke 3.2%; lifethreatening bleeding 15.6%; major vascular complication 11.9%; renal injury 7.5%; and MI 1.1%) (39) do **not** appear to **favor prophylactic TAVR** in **asymptomatic severe AS** patients undergoing noncardiac surgery.

Advances in surgical and anesthetic techniques (avoidance of intraoperative hypotension and treating it aggressively with phenylephrine, avoidance of tachycardia with aggressive management of intraoperative arrhythmia) with closer perioperative monitoring appear to have made performance of noncardiac procedures possible with acceptable risk in these patients.

At least for "asymptomatic severe aortic stenosis" patients with preserved LV systolic function and no other significant valvular pathology, a reappraisal of the grading of the severity of AS in general and reassessment of perioperative risk during noncardiac surgery is urgently needed.

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