

STATE-OF-THE-ART PAPER

Is Aortic Stenosis a Preventable Disease?

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Aortic stenosis (AS) is the most common valvular disease requiring valve replacement. Its prevalence increases with age. When the severity of AS is only mild to moderate, it is well tolerated. When it becomes severe, AS confers significant morbidity and mortality. Adverse events can be avoided if it is possible to prevent or retard the progression from mild or moderate AS to severe AS. Progression of AS parallels the progression of sclerotic changes involving the aortic valve, which share histological and immunochemical similarities with the process of atherosclerosis. Far from being just a degenerative process, the development of AS is a complex and highly regulated process with a number of modifiable factors. One of the key factors appears to be lipoproteins, which are intimately involved in several pathways crucial to the development of AS. The importance of lipoproteins is further supported by epidemiological and clinical studies showing a strong association between lipoproteins and AS. The time has come to initiate prospective studies to assess the effect of cholesterol lowering on the progression of AS. (J Am Coll Cardiol 2003;42:593-9) © 2003 by the American College of Cardiology Foundation

Aortic stenosis (AS) is the most common valvular disease in the western world (1-3). It is associated with significant mortality and morbidity. The prevalence increases with age such that it affects about 3% of the elderly population and is the most common reason for valve replacement (1-4). It will be an increasingly important health issue in view of the improving life expectancy of the population. Mild to moderate AS is well tolerated and usually produces no symptoms (5,6). On the other hand, severe AS is associated with significant morbidity and mortality, and valve replacement is generally required (3,4). An effective strategy to prevent or retard the progression from mild or moderate AS to severe AS should yield major health benefits.

HISTOLOGY OF AS

Over the past 30 years, dramatic changes in the etiology of AS have occurred. In developed countries, the number of patients with rheumatic AS has dwindled, and the main types of the condition are now calcific bicuspid and tricuspid AS (1-3). The histologic findings of nonrheumatic AS are well recognized (7-11). The "early lesions" in mild AS valves are characterized by subendothelial thickening with disruption of the basement membrane, accumulation of intra- and extracellular lipids, and cellular infiltration with macrophages (9-12). The adjacent fibrosa is thickened and demonstrates accumulation of protein, lipid, and calcium. Both foam cell and non-foam cell macrophages are present. The abnormalities are concentrated on the aortic side of the non-coaptational portion of the cusps, and more marked in valves with severe AS (7-12). The cusps of severe AS valves

are diffusely thickened with degeneration of structural components. Macroscopic calcific nodules are invariably present and located at the area of maximal cusp flexion, restricting cusp excursion. These abnormalities result in thickened and stiff cusps that have little systolic excursion, leading to obstruction of left ventricular outflow (7-11).

In adult patients, the dominant feature of severe AS, be it bicuspid aortic valve (BAV) or tricuspid aortic valve (TAV), is the presence of calcification, which can be quite extensive (1-3,13). Although it has been suggested that the distribution of calcific deposits may be different in BAVs versus TAVs, pathologic examination of large numbers of these valves have shown more similarities than differences (14). In BAV, calcification tends to be nodular and localized at the raphe and the base of the valve pockets. In TAV, calcification can be nodular but at times more diffuse, and is localized in the valve pockets and the base of the commissures. Nodular calcification on the TAV is uncommon before the age of 50 but is frequently detected in younger patients with BAV (4,15,16). The progression of dystrophic calcification is more rapid such that AS is a common complication in BAV patients leading to aortic valve replacement at a younger age compared with patients with tricuspid AS (1,16). On average patients with BAV requiring surgery for AS are a decade younger than those with tricuspid stenosis, likely related to the propensity for development of calcification at an earlier age (1-3,13).

Thus, a wide range of abnormalities can be seen in AS valves, starting with small areas of fibrosis and thickening to extensive structural degeneration, nodular thickening, and dystrophic calcification. These changes appear to be progressive over a number of years and, when severe, are closely associated with severe AS. The reasons these changes are progressive in some patients and relatively static in others have not been defined.

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Abbreviations and Acronyms

- AS = aortic stenosis
- BAV = bicuspid aortic valve
- LDL = low-density lipoprotein
- TAV = tricuspid aortic valve
- TGF = transforming growth factor

PATHOGENESIS OF AS

The conventional view is that AS is a “degenerative” process, with the valve damage being a result of wear and tear (1,15,17). Hydrodynamic studies have shown that there is flow disturbance and near stagnation at the aortic side of the aortic cusps (17,18). A high mechanical stress occurs at the flexion area of the aortic cusps near the attachment to the aorta root and the line of coaptation (17,18). Aortic endothelium at areas of high mechanical stress demonstrates subtle changes consistent with mild damage and becomes more susceptible to lipid deposition and infiltration by macrophages. This process is accelerated in BAV because the abnormal cusps and raphe are subject to greater mechanical stress (1).

However, only a minority of elderly individuals develop AS, and AS is not necessarily an inevitable outcome even in those with BAV (4,16). Factors other than age-related degeneration must be involved in the development of AS. Recent studies show that changes in AS are similar to those in atherosclerosis (Table 1) (12,19-29). The latter also increases with age but is clearly more than just a degenerative process. An intricate interaction of multiple processes have been demonstrated to be operative in AS valves, such as evidence of chronic inflammation including the presence of macrophages and T-lymphocytes (9,12,21), accumulation of apolipoproteins in addition to lipids (12,20,22,23), detection of proteins such as osteopontin implicated in calcification (24), and the detection of calcifying valve cells with osteoblast-like activities (25,26). These findings suggest that the development of AS is a highly regulated, active

Table 1. Comparison of Sclerotic Process in Aortic Stenosis With That in Atherosclerosis

	Aortic Stenosis	Atherosclerosis
Inflammatory changes	+	++
Calcifying cells and mediators	+	+
Calcification	++	+
Heterotopic ossification	+	+
Lipoproteins	+	+
Oxidized lipids	+	+
Role of smooth muscle	-	+
Role of infective agents	±	±

+ = present; ++ = prominent feature; - = absent; ± = suggestive.

process, which is potentially modifiable, rather than being an inevitable outcome of aging.

CELLULAR AND MOLECULAR PROCESSES IN AS

Increased valve thickness is a requisite finding in AS, caused by the combined effect of increased cellularity, lipid accumulation, and extracellular matrix deposition (9,12). Calcification is also a dominant feature, particularly when AS is severe (1,9). Recent studies have provided insights into the cellular and subcellular mechanisms underlying these macroscopic changes. Figure 1 illustrates the multiple pathways in the genesis of valvular AS, with lipoproteins being a key component in many of these pathways (19,20). The initiating event appears to be endothelial injury at areas of mechanical stress, predisposing to infiltration by plasma lipoproteins similar to what is known to happen in the development of atherosclerosis in susceptible arterial walls (17,18). Another intriguing possibility is that the sequence of events may be triggered by an infective organism such as *Chlamydia pneumoniae*, which can be detected in half of the AS valves, but the role of infective agents in AS requires further studies (27,28). Stenotic “degenerative” aortic valves have a much larger amount of lipids than non-stenotic valves (12). Lipid deposition tends to be localized to the aortic surface of the flexion areas, which are under high mechanical strain and lower shear stress. The abnormal mechanical forces are likely to be more prominent in BAV, leading to a greater degree of lipid deposition at an earlier age. Co-localization of components of atherogenic apolipoproteins (apo-B, apo-[a], and apo-E) has been demonstrated in close proximity to the extracellular lipids, strongly suggesting that the lipid deposits are derived from plasma lipoproteins (20,23). This is followed by oxidative modification, and after more extensive modification the oxidized particles are taken up by macrophages to form foam cells (12,23). Oxidized low-density lipoprotein (LDL) has been shown to have prothrombotic effects, as well as to be highly cytotoxic for many cells, including endothelial cells and valve fibroblasts. It is suggested that fibroblasts, upon exposure to oxidized LDL, release matrix vesicles which form the nidus for calcification (24,25,30). Apolipoprotein deposition in early AS lesions resembles closely the process in early lesions of atherosclerosis (12). It has a predilection for areas of low shear stress and is associated with accumulation of macrophages, T-lymphocytes, and matrix proteins such as proteoglycans (12,20).

In addition to macrophages, a large number of T-lymphocytes are present in the subendothelial and fibrosa layers of stenotic valves (12,21). They co-localize near calcific nodules. T-lymphocytes appear to play an important part in the development of AS. They are activated, as evidenced by the expression of interleukin II receptors. They release several cytokines, including transforming growth factor (TGF)-beta, which is a potent activator of extracellular matrix formation. Recently the presence of calcifying

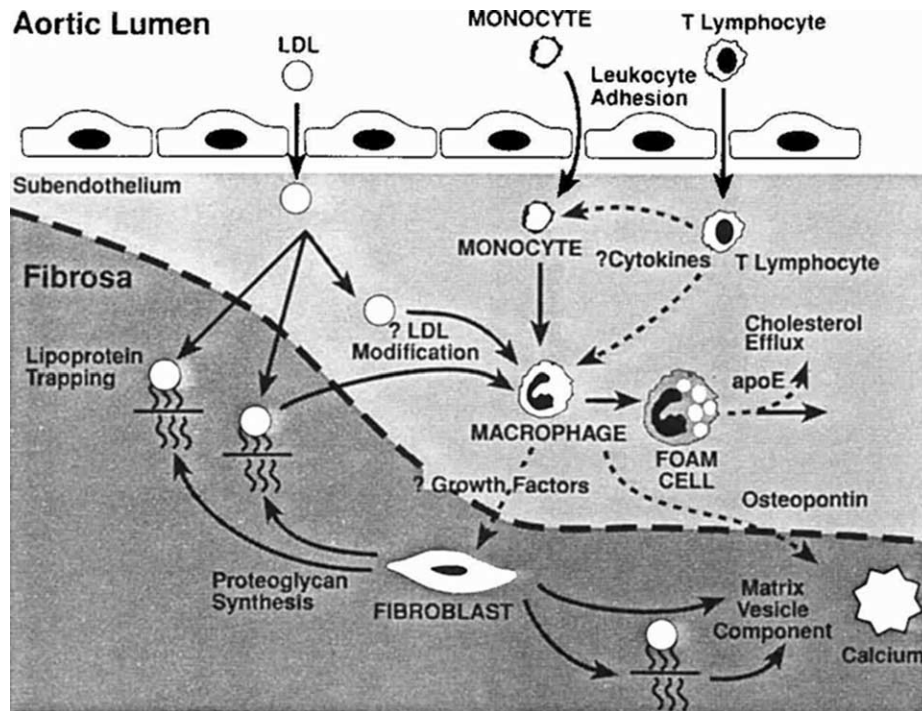


Figure 1. Pathogenetic mechanisms in aortic valve stenosis. Lipoproteins are involved in multiple pathways, which lead to fibrosis and calcification. From O'Brien et al. (20), *Arterioscler Thromb Vasc Biol* 1996, reprinted with permission. LDL = low-density lipoprotein.

valve cells has been demonstrated in stenotic valves (25,26). The origin of these cells is still unclear, but they appear to be a population of interstitial cells that naturally reside in cardiac valves. These cells undergo a phenotypic transformation to become osteoblast-like cells that spontaneously form calcific nodules (25,26). Their activities are modulated by growth factors including TGF-beta and hydroxycholesterol, which is one of the oxidized sterols (25,26,31). Under the stimulation of growth factors, these cells produce proteins that are instrumental in calcification. These include osteopontin, osteonectin, and alkaline phosphatase. Fibroblasts in AS valves appear to be different from fibroblasts in normal valves in that they secrete alpha-actin and desmin in addition to vimentin (30). The majority of these cells also express histocompatibility antigens (HLA-DR molecules) usually associated with immunocompetent cells (24). In addition, fibroblasts may be capable of releasing cytokines, including osteopontin, and likely play an important role in the development of fibrosis and calcification, which are found commonly in AS valves. Furthermore, endochondral bone formation may occur (24,29).

The findings of these recent studies demonstrate a close association between lipids and calcification, both of which are invariably present in stenotic valves. The sclerosing process in aortic valves is a complicated one, but lipids appear to play an integral part, as they are involved in multiple pathways required for the development of fibrosis and calcification. These observations underscore that AS may not be an inevitable degenerative process of aging, but rather is an active process that involves multiple pathways and is thus potentially modifiable (6,11).

LIPIDS AND AS

Animal models. The effect of hypercholesterolemia on the development of sclerotic changes involving the heart valves has been demonstrated. Rats on an atherogenic diet for up to 15 months showed prominent lipid plaques on the aortic surface of aortic cusps near the attachment to the aortic wall, which are the typical areas of involvement in human AS (32). Sarphie (33) studied the topographic changes of the aortic valve in rabbits on a cholesterol-enriched diet and showed that there were dramatic changes in the endothelial cells lining the arterial surfaces but not those lining the ventricular surface of the aortic cusps. The changes included a corrugated endothelial surface contour, interendothelial fenestra, and subendothelial foam cells. A recent study showed that mice with hyperlipidemia due to over expression of apolipoprotein E4 all developed severe AS in addition to coronary disease (34). Finally, in rabbits on a high-cholesterol diet, sclerotic changes of the aortic valve, including a large number of foam cells, have been shown. Osteopontin expression was also detected. This proliferative atherosclerosis-like process can be inhibited by a statin (35).
Clinical evidence. Valvular and supravalvular AS are well known in subjects with familial hypercholesterolemia (36-39), and AS may regress with aggressive reduction of serum cholesterol. In fact, sclerotic changes of the aortic valve are ubiquitous in homozygotes and common in heterozygotes (40). The histological picture of AS in these patients bears close resemblance to that of calcific "degenerative" AS (38-40).

In view of the similarity in histology between the scler-

Table 2. Risk Factors Associated with Aortic Stenosis

Author	Study Design	n	Mean Age (yrs)	Positive Risk Factors
Deutscher et al. (1983) (41)	Case control	54 cases 359 controls	NA NA	Hypercholesterolemia, diabetes
Hoagland et al. (1985) (42)	Case control	105 cases (41 BAV) 439 controls	66	None
Aronow et al. (1987) (43)*	Hospital survey	571	82	Hypertension, hypercholesterolemia, diabetes, low HDL cholesterol
Mohler et al. (1991) (44)	Retrospective	39 BAV 30 degenerative	62 72	Race, gender, low triglyceride, smoking
Lindroos et al. (1994) (45)*	Prospective	501	>75	Hypertension, low BMI
Boon et al. (1997) (46)	Retrospective echo database	515 cases 562 controls	67	Age, hypertension, hypercholesterolemia
Stewart et al. (1997) (47)*	Prospective	5,201	73	Gender, age, hypertension, lipoprotein (a), LDL cholesterol
Wilmshurst et al. (1997) (48)	Prospective case control	20 cases (6 BAV) 20 controls	66	Cholesterol
Chan et al. (2001) (49)	Prospective case control	48 cases (all BAV) 52 controls (all BAV)	56	Cholesterol, history of hypertension
Aronow et al. (2001) (50)	Retrospective	180 cases	82	Gender, smoking, hypertension, diabetes, cholesterol, not on statin
Chui et al. (2001) (51)	Retrospective case control	43 cases (18 BAV) 40 controls	66	Cholesterol
Peltier et al. (2003) (52)	Prospective case control	220 cases 220 controls	68	Hypertension, smoking, high BMI, cholesterol

*Includes cases with sclerotic changes of the aortic valve and/or aortic root.

BAV = bicuspid aortic valve; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not available.

rosing process of AS and atherosclerosis, it is logical to presume that risk factors for atherosclerosis may also be important in the development of AS. The studies looking at the association of atherosclerotic risk factors with AS are summarized in Table 2 (41–52).

The two early case control studies showed contradictory results (41,42). In both studies, the cases and the control subjects were largely drawn from patients referred for cardiac catheterization and thus expected to have a high prevalence of atherosclerotic risk factors. The studies by Aronow et al. (43,50) examined patients over 80 years of age in a chronic care facility, and the prospective study by Lindroos et al. (45) dealt with subjects at least 75 years of age. The results of these two studies are obviously limited in terms of their generalizability. The largest prospective study in this regard is the Cardiovascular Health Study. This population-based study of the elderly, with extensive clinical and echocardiographic data, reported a positive association of aortic valve disease, which comprised of AS in 2% and aortic sclerosis in 26% of the total cohort, with risk factors including age, male gender, history of hypertension, and high lipoprotein (a) and LDL cholesterol levels (47). In a retrospective study, Mohler et al. (44) compared risk factors for AS in BAV versus TAV in surgical patients who had aortic valve replacement for AS. Race, male gender, and low triglyceride levels were correlated with age at surgery in bicuspid AS, whereas male gender and smoking were the risk factors for patients with degenerative tricuspid AS.

Many of the studies looking at atherosclerotic risk factors in AS are limited by the use of retrospective data, varying definition of aortic valve disease, and referral bias. In only

five of these studies was the morphology of the aortic valve specifically assessed. Bicuspid aortic valve accounted for 39% of the AS cases in the case control study of Hoagland et al. (42) and 57% of the surgical-pathologic study of Mohler et al. (44), 42% of the surgical series by Chui et al. (51), and 0% in the case control study of Peltier et al. (52). The study by Wilmshurst et al. (48) found that cholesterol was higher in patients with AS compared with controls. The patients had severe AS and were drawn from those referred for cardiac catheterization. Only triglyceride and cholesterol levels were compared between the two groups. Peltier et al. (52) included only patients with calcific TAV, and the valve morphology was confirmed at surgery in all cases. The controls in their study were patients who required valve surgery for valvular regurgitation. They showed that total cholesterol >200 mg/dl, in addition to hypertension, smoking, and a high body mass index were associated with AS. However, they did not assess the effects of the different cholesterol components, including LDL and high-density lipoprotein cholesterol levels.

The general lack of appreciation of the significance of BAV in patients with AS is intriguing and likely related to the difficulty in reliably detecting BAV before surgery or autopsy examination. We prospectively identified 100 patients with BAV from patients referred to our center for echocardiographic assessment (49). Bicuspid aortic valve patients with AS were matched with BAV patients with no significant stenosis. We showed that total cholesterol was the most significant risk factor for AS (odds ratio 1.77, $p = 0.01$), despite relatively normal cholesterol levels in both groups (5.5 ± 1.1 mmol/l in cases vs. 4.9 ± 0.9 mmol/l in

Table 3. Studies on Progression of Aortic Stenosis

Author	Method	n	Mean Age (yrs)	Follow-Up (yrs)	Baseline Gradient	Increase in Gradient (mm Hg/yr)	Decreased in AVA (cm ² /yr)	Risk Factors for Progression
Cheitlin et al. (1979) (58)	Catheter	29	45	3.6	34	7.6	NA	Progressive symptom
Wagner and Selzer (1982) (59)	Catheter	50	54	3.5	38	5.4	NA	Age, AV calcification
Nitta et al. (1987) (60)	Catheter	11	NA	3.0	23	7.7	NA	Age
Turina et al. (1987) (61)	Catheter	29	NA	7.0	50	3.4	NA	None
Otto et al. (1989) (62)†	Doppler	42	66	1.7	35	8.0	0.10	Female, symptoms
Roger et al. (1990) (63)	Doppler	112	69	2.1	35*	4.8*	NA	Female, symptoms
Davies et al. (1991) (5)	Catheter	65	54	7.0	10	6.5	NA	AV calcification
Faggiano et al. (1992) (64)	Doppler	45	72	1.5	64*	15.0*	0.10	Baseline pressure gradient
Peter et al. (1993) (65)	Doppler	49	58	2.6	38*	7.2*	NA	Age, CAD
Ilvanainan et al. (1996) (66)†	Doppler	333	81	3.0	7	NA	0.06	BMI
Otto et al. (1997) (6)†	Doppler	123	63	2.5	29	7.0	0.12	Baseline pressure gradient, symptoms
Bahler et al. (1999) (67)	Doppler	91	68	1.8	16	4.9	0.08	AV calcification, baseline AVA
Palta et al. (2000) (68)	Doppler	170	71	2.0	20	7.0	0.10	Baseline AVA, smoking, serum calcium
Ngo et al. (2001) (69)	Doppler	123	70	2.5	31*	6.3*	NA	History of smoking, BMI
Novaro et al. (2001) (70)	Doppler	174	68	1.8	15	NA	0.11	Age, not on statin
Bellamy et al. (2002) (71)	Doppler	156	77	3.7	21	5.3	0.06 (on statin) 0.09	Not on statin
						2.9 (on statin)	0.04 (on statin)	

*Peak gradient. †Prospective studies.

AV = aortic valve; AVA = aortic valve area; BMI = body mass index; CAD = coronary artery disease.

controls). An important aspect of our study is that these were largely ambulatory, asymptomatic, young patients (mean age 56 years).

Taken together, these studies showed that atherosclerotic risk factors, particularly hypercholesterolemia, are associated with calcific AS in both BAVs and TAVs. However, there are differences between the processes underlying AS and atherosclerosis (Table 1). Only one-half of the patients with AS have coronary artery disease, and a minority of patients with coronary artery disease have concomitant AS (53). Factors accounting for the discordance between the two processes have not been well defined, but may be related to the presence of other pathways, such as those involving the angiotensin-converting enzyme and vitamin D, both of which have been implicated in the development of AS (54,55). A recent study suggested that the B allele of the vitamin D receptor may be a predisposing factor for AS (55). Future studies will likely identify other genetic markers specific to the process of AS or atherosclerosis.

PROGRESSION AND CLINICAL SIGNIFICANCE OF AS

Recent evidence suggests that aortic sclerosis is a common finding in the elderly and a precursor of AS (56,57). Faggiano et al. (56) reported that about one-third of the patients with aortic sclerosis developed some degree of AS in a follow-up of four years. When mild or moderate AS ensues, the overall rate of progression becomes more predictable at about 7 mm Hg increase in mean gradient per

year, although substantial variability occurs in individual patients (58–71). Table 3 summarizes the results of studies that have examined this question.

In the older studies, the observations were based on catheter-derived hemodynamic data (5,58,59), whereas the more recent studies obtained these parameters using non-invasive Doppler echocardiography (6,60–71). Only three of these studies were prospective in nature (6,62,66). The annual increase in the aortic valve gradient was quite similar among the different studies, averaging about 7 mm Hg per year, despite the differences in study design, baseline aortic valve gradients, and the duration of follow-up. Factors predictive of a more rapid progression have been proposed. Palta et al. (68) found that initial aortic valve area, current smoking, and serum calcium level were positively correlated with AS progression in 170 patients who had paired echocardiograms. Patients with cholesterol level >200 mg/dl had twice the rate of progression compared with those with lower cholesterol level, although cholesterol was not an independent predictor in the multiple regression analysis. In the study by Novaro et al. (70), the predictors for more rapid progression were age and not being on statin therapy. The annualized decreases in aortic valve area were 0.11 cm² in the patients not taking a statin and 0.06 cm² in those on a statin. There was a modest relationship between the change in LDL cholesterol level and the change in aortic valve area. Bellamy et al. (71) also showed an association between statin use and slower AS progression,

but they did not find a significant correlation between progression of AS and the cholesterol levels. It is noteworthy that the morphology of aortic valve, that is BAV versus TAV, was not examined in most of these studies, likely because of the inability to determine valvular morphology by cardiac catheterization or even by echocardiography. In the studies of Otto et al. (6) and Bellamy et al. (71), the rate of progression in AS severity was no different in those with a BAV versus TAV.

Recent studies utilizing electron beam tomography provide further evidence to support the importance of cholesterol in the genesis of AS. Calcification of aortic cusps, invariably present in adults with AS, can be quantitated by electron beam tomography (72,73). Pohle et al. (73) showed a positive correlation between LDL cholesterol level and progression of aortic valve calcification. Treatment with a statin appears to reduce the progression of aortic valve calcification. In the study of Shavelle et al. (72), statin treatment reduced almost by half the number of patients with progression of aortic valve calcification in a mean interval of 2.5 years.

Summary. Aortic stenosis is the most common valvular disease, but adverse events are uncommon until the development of severe AS (63-65). Regular follow-up of AS patients is important to monitor hemodynamic progression and development of symptoms. Recent studies showed that AS is an active process, which is highly regulated and potentially modifiable. Lipids appear to play an important role in the development and progression of AS, and there is mounting evidence that cholesterol lowering may retard or prevent the progression. An effective medical strategy to slow or stop the progression of AS will have major public health benefits, in view of higher prevalence of AS with age and increasing life expectancy of the general population. Prevention of the development of severe AS is a novel idea, which has not been tested. The time has come for such a study in patients with mild to moderate AS. The result of the study will have a direct impact on the treatment of AS patients and will expand our understanding of the pathogenesis of AS.

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