JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 15, 2020

PUBLISHED BY ELSEVIER

Transvalvular Flow Rate Determines Prognostic Value of Aortic Valve Area in Aortic Stenosis

Mayooran Namasivayam, MBBS, PhD,[a] Wei He, MSc,[a] Timothy W. Churchill, MD,[a] Romain Capoulade, PhD,[a,b,c] Shiying Liu, MD,[a] Hang Lee, PhD,[a] Jacqueline S. Danik, MD, DrPH,[a] Michael H. Picard, MD,[a] Philippe Pibarot, DVM, PhD,[c] Robert A. Levine, MD,[a] Judy Hung, MD[a]

ABSTRACT

BACKGROUND Aortic valve area (AVA) ≤1.0 cm^2 is a defining characteristic of severe aortic stenosis (AS). AVA can be underestimated at low transvalvular flow rate. Yet, the impact of flow rate on prognostic value of AVA ≤1.0 cm^2 is unknown and is not incorporated into AS assessment.

OBJECTIVES This study aimed to evaluate the effect of flow rate on prognostic value of AVA in AS.

METHODS In total, 1,131 patients with moderate or severe AS and complete clinical follow-up were included as part of a longitudinal database. The effect of flow rate (ratio of stroke volume to ejection time) on prognostic value of AVA ≤1.0 cm^2 for time to death was evaluated, adjusting for confounders. Sensitivity analysis was performed to identify the optimal cutoff for prognostic threshold of AVA. The findings were validated in a separate external longitudinal cohort of 939 patients.

RESULTS Flow rate had a significant effect on prognostic value of AVA. AVA ≤1.0 cm^2 was not prognostic for mortality ($p = 0.15$) if AVA was measured at flow rates below median (≤242 ml/s). In contrast, AVA ≤1.0 cm^2 was highly prognostic for mortality ($p = 0.003$) if AVA was measured at flow rates above median (>242 ml/s). Findings were irrespective of multivariable adjustment for age, sex, and surgical/transcatheter aortic valve replacement (as time-dependent covariates); comorbidities; medications; and echocardiographic features. AVA ≤1.0 cm^2 was also not an independent predictor of mortality below median flow rate in the validation cohort. The optimal flow rate cutoff for prognostic threshold was 210 ml/s.

CONCLUSIONS Transvalvular flow rate determines prognostic value of AVA in AS. AVA measured at low flow rate is not a good prognostic marker and therefore not a good diagnostic marker for truly severe AS. Flow rate assessment should be incorporated into clinical diagnosis, classification, and prognosis of AS. (J Am Coll Cardiol 2020;75:1758–69)

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From the [a]Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [b]Université de Nantes, CHU Nantes, CNRS, INSERM, l'institut du thorax, F-44000, Nantes, France; and the [c]Quebec Heart and Lung Institute, Laval University, Quebec City, Quebec, Canada. This work was presented by Dr. Namasivayam at the Samuel A. Levine Early Career Clinical Investigator Award Competition at the American Heart Association Scientific Sessions, November 2019. Dr. Namasivayam has received a travel stipend and honorarium from the American Heart Association and the St. Vincent's Clinic Foundation Traveling Fellowship Award; and is supported by a Clinical and Research Fellowship from the Division of Cardiology, Massachusetts General Hospital, Harvard Medical School. Dr. Capoulade is supported by a Connect Talent Research Chair from Région Pays de la Loire and Nantes Métropole. Dr. Pibarot is supported in part by grants FDN-143225 and MOP-114997 from Canadian Institutes of Health Research (CIHR) and a grant from the Foundation of the Quebec Heart and Lung Institute; has received funding from Edwards Lifesciences and Medtronic for echo corelab or in vitro analyses with no personal compensation; and holds the Canada Research Chair in Valvular Heart Diseases from CIHR. Dr. Hung is supported in part by grants R01 HL092101 and U01 HL088942 from the National Heart, Lung, and Blood Institute. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 19, 2019; revised manuscript received February 1, 2020, accepted February 14, 2020.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2020.02.046

Aortic stenosis (AS) is a major cause of morbidity and mortality, and is projected to increase in prevalence in the context of aging populations (1). With easier access to valve replacement therapy (2), the significant uncertainty about true stenosis severity in a large proportion of AS patients, such as low-gradient AS, mandates a careful approach to diagnosis and prognostication (3). Aortic valve area (AVA), measured by Doppler echocardiography and application of the continuity equation, is a central criterion of AS assessment (4–6). The threshold AVA to define severe AS has been set as 1.0 cm^2 (≤1.0 cm^2 in Europe and <1.0 cm^2 in the United States) (4,5).

SEE PAGE 1770

Flow state is important in the assessment of AS. Current assessment of flow uses a volume-based metric (stroke volume index [SVi]) (7). However, volume is fundamentally different to flow, the latter defined as volume *per unit time* (transvalvular flow rate) (8). AVA measurement is highly dependent on transvalvular flow rate (Q), the ratio of stroke volume (SV) to ejection time (ET) (9–11). Q represents the mean volume of blood passing through the aortic valve per unit of time during ventricular ejection.

Maximal (or "true") AVA (which would be measured under normal flow conditions) may not be induced at low Q due to inadequate valve opening. Hence, AVA at low Q is not necessarily representative of true stenosis severity. Despite this, the effect of Q on prognostic value of AVA remains unknown and is thus unaccounted for in current guidelines. No study to date has evaluated the impact of flow state on the prognostic value of AVA in AS.

We aimed to evaluate the effect of Q on prognostic value of AVA for mortality in AS. We hypothesized that Q modifies the prognostic value of AVA in AS, such that low AVA (≤1.0 cm^2) determined at low Q would be less prognostic than if measured at high Q. We additionally sought to validate findings in a separate, longitudinal cohort, and assess the value of quantifying flow state using Q versus stroke volume.

METHODS

PRIMARY COHORT. We included patients with moderate or severe AS defined by AVA ≤1.5 cm^2 or mean gradient ≥20 mm Hg who underwent echocardiography between 2006 and 2016. Moderate AS was included as a referent group for nonsevere AS. Quantitative data were determined from values reported in the official clinical read by an attending cardiologist with level III certification in echocardiography. We excluded patients with aortic valve prostheses, left ventricular outflow tract velocity ≥1.6 m/s, moderate or greater aortic regurgitation, moderate or greater mitral regurgitation, supravalvular or subvalvular aortic stenosis, aortic coarctation, or aortic dissection. In total, 3,404 unique patients were identified. From this group, we evaluated patients whose primary care was longitudinally based at our center, meaning that their clinical follow-up data was complete for this study. This left 1,131 patients for analysis (Supplemental Figure 1). Baseline comorbidities and medications were determined using the electronic health record. Aortic valve replacements by open surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR) were identified using the Current Procedural Terminology coding system. Mortality data was obtained from the electronic health record, which integrated social security and clinical death records to identify dates of death. Despite this integrated system, date of death could not be determined in 1 patient. A patient's first available echocardiogram in the study period was used to source echocardiographic data.

In each patient, we calculated the Q, which is traditionally defined by the ratio of stroke volume to ejection time: Q = SV/ET. The echocardiography database did not routinely record SV or ET; therefore, we calculated Q with a mathematically equivalent method using the available data as explained in the Supplemental Appendix. In brief, the derivation method utilizes the principle that Q is not only the ratio of volume to time, but also the product of area and mean velocity (Supplemental Figure 2). We validated our derivation method against Q measured using SV and ET in our validation cohort (Supplemental Figure 3).

STATISTICS. Patients were stratified by Q above and below the median. We compared baseline characteristics using the 2-tailed Student's *t*-test for normally distributed data, Mann-Whitney *U* test for non-normal data (assessed by skewness statistic <−0.5 or >0.5) and chi-square test for proportions. We compared the prognostic value of AVA ≤1.0 cm^2 at Q above and below the median using Cox proportional hazards models. Models for time to death (all-cause mortality) were adjusted for age, sex, and aortic valve replacement (SAVR or TAVR), including time to SAVR or TAVR using time-dependent covariate analysis. We made further multivariable adjustment for baseline comorbidities,

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
AVA = aortic valve area
EF = ejection fraction
ET = ejection time
LVOT = left ventricular outflow tract
Q = transvalvular flow rate
SAVR = surgical aortic valve replacement
SV = stroke volume
SVi = stroke volume index
TAVR = transcatheter aortic valve replacement

TABLE 1 Baseline Characteristics by Flow Rate

	Below Median Q (n = 566)	Above Median Q (n = 565)	Sig.
Demographics			
Age, yrs	78.9 ± 10.5	74.5 ± 11.0	<0.001
Male	269/566 (47.5)	408/565 (72.2)	<0.001
White race	511/566 (90.3)	531/565 (94.0)	NS (0.24)
Body surface area, m^2	1.8 ± 0.2	2.0 ± 0.2	<0.001
Comorbidities			
Diabetes mellitus	160/566 (28.3)	177/565 (31.3)	NS (0.26)
Hypertension	484/566 (85.5)	470/565 (83.2)	NS (0.28)
Heart failure	207/566 (36.6)	151/565 (26.7)	<0.001
Coronary artery disease	220/566 (38.9)	182/565 (32.2)	0.019
Myocardial infarction	130/566 (23.0)	105/565 (18.6)	NS (0.07)
Peripheral vascular disease	227/566 (40.1)	220/565 (38.9)	NS (0.69)
Hyperlipidemia	50//566 (89.8)	504/565 (89.2)	NS (0.76)
Atrial fibrillation	199/566 (35.2)	130/565 (23.0)	<0.001
Chronic kidney disease	171/563 (30.4)	126/559 (22.5)	0.003
Never smoked	156/483 (32.3)	139/483 (28.7)	NS (0.42)
Medications			
Beta-blocker	388/566 (68.6)	355/565 (62.8)	0.043
ACE inhibitor	264/566 (46.6)	264/565 (46.7)	NS (0.98)
ARB	106/566 (18.7)	109/565 (19.3)	NS (0.81)
Potassium-sparing diuretic agents	30/566 (5.3)	23/565 (4.1)	NS (0.33)
Calcium-channel blocker			
Dihydropyridine	168/566 (29.7)	166/565 (29.4)	NS (0.91)
Nondihydropyridine	56/566 (9.9)	54/565 (9.6)	NS (0.85)
Nitrate	148/566 (26.1)	138/565 (24.4)	NS (0.51)
Statin	433/566 (76.5)	421/565 (74.5)	NS (0.44)
Antiplatelet	422/566 (74.6)	415/565 (73.5)	NS (0.67)
Oral anticoagulant	164/566 (29.0)	130/565 (23.0)	0.022
Echocardiographic data			
AVA, cm^2	0.90 ± 0.23	1.16 ± 0.23	<0.001
Mean gradient, mm Hg	28.2 ± 14.0	30.8 ± 13.3	<0.001
Q, ml/s	203.4 ± 28.8	283.6 ± 37.0	<0.001*
Peak gradient, mm Hg	49.9 ± 22.3	53.7 ± 21.6	<0.001
Bicuspid	34/566 (6.0)	56/565 (9.9)	0.02
LVEDD, mm	42.6 ± 6.5	44.5 ± 6.2	<0.001
LVESD, mm	28.7 ± 7.3	28.6 ± 5.9	NS (0.34)
Ejection fraction	62.8 ± 13.8	67.8 ± 9.5	<0.001
Aortic sinus diameter, mm	31.3 ± 4.2	33.5 ± 3.9	<0.001
Ascending aortic diameter, mm	33.1 ± 4.6	35.0 ± 4.6	<0.001
Interventricular septal thickness, mm	12.3 ± 2.2	12.7 ± 2.2	0.006
Posterior wall thickness, mm	11.2 ± 1.9	11.4 ± 1.9	NS (0.06)
LA anteroposterior dimension, mm	39.3 ± 6.5	39.9 ± 6.2	NS (0.11)
LVOT diameter, cm	2.01 ± 0.18	2.17 ± 0.18	<0.001
LVOT velocity, m/s	0.95 ± 0.19	1.12 ± 0.18	<0.001

Median Q 242 ml/s. *The data presented in this table are dichotomized by median flow rate; therefore, the p value for this variable is shown for illustrative purposes only.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AVA = aortic valve area; LA = left atrium; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LVOT = left ventricular outflow tract; NS = not significant; Q = transvalvular flow rate.

medications, and echocardiographic features that were significantly different at baseline between patients with Q above and below the median.

Effect modification of Q on AVA's prognostic value was confirmed using measurement of interaction effect for mortality prediction above and below the median Q.

Sensitivity analysis was performed to identify the lowest Q threshold above which prognostic significance of AVA ≤1.0 cm^2 for mortality was maintained.

Where analyses note comparisons between Qs above and below the median, exact dichotomization was such that below median represents ≤ median, whereas above median represents > median. The same applies to the validation cohort.

Statistical analyses were performed using IBM SPSS version 25 (IBM Corporation, Armonk, New York).

VALIDATION COHORT. The validation cohort was comprised of patients from a previously described longitudinal cohort from the Quebec Heart and Lung Institute, Canada (6). From the original 1,065 patients, 116 were excluded for not meeting inclusion criteria (AVA ≤1.5 cm^2 or MG [mean gradient] ≥20 mm Hg) and 10 were excluded for missing transvalvular gradient data, leaving 939 patients. Using Cox proportional hazards models, we again evaluated the impact of Q on prognostic value of AVA. In the validation cohort where both derived and measured Q were available, references to Q refer to derived Q unless otherwise specified.

ETHICS APPROVAL. Studies were approved by the Massachusetts General Hospital/Partners Institutional Review Board and the Ethics Committee of the Quebec Heart and Lung Institute. Informed consent was not required.

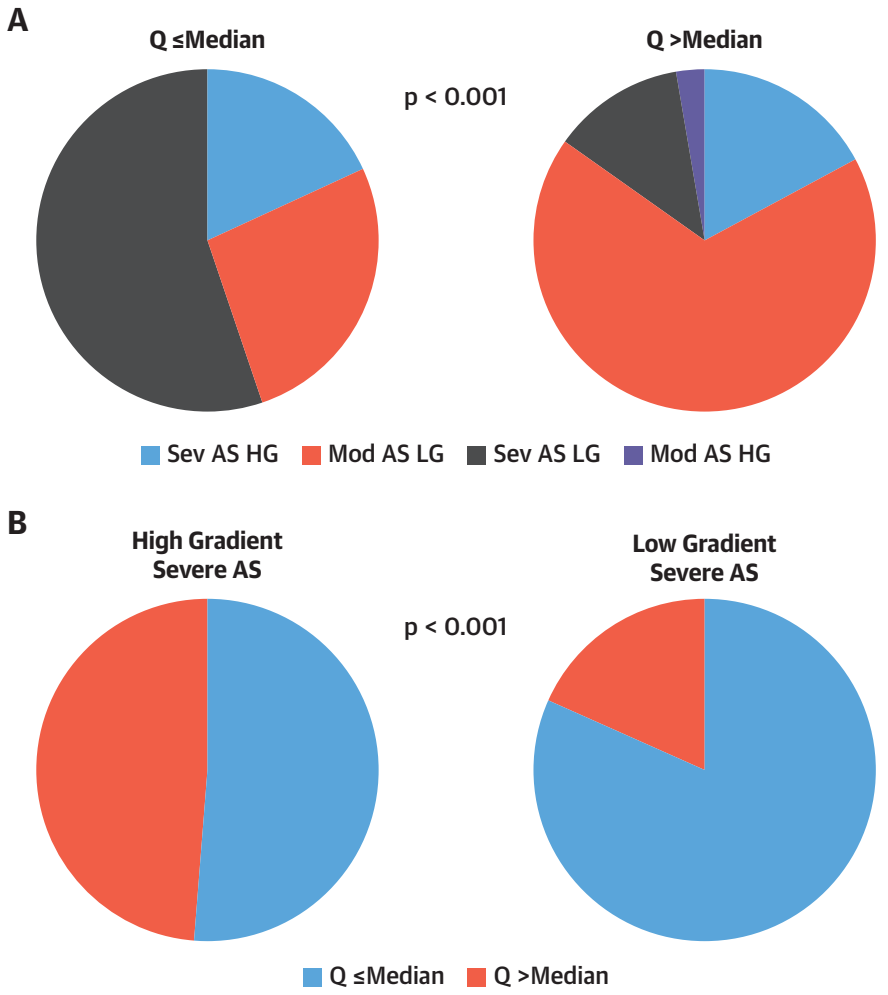
RESULTS

PRIMARY COHORT. In the primary cohort (n = 1,131; 60% male), mean age was 77 ± 11 years. Q was normally distributed, with mean Q 243 ± 52 ml/s and median Q 242 ml/s (Supplemental Figure 4). Baseline characteristics are shown in **Table 1** stratified by Q above and below the median. Patients with Q below the median (Q ≤ 242 ml/s) were typically older and had more comorbidities. Left ventricular ejection fraction (EF) was normal in the majority of the cohort (91% of patients had EF ≥50%).

In patients with low-gradient severe AS, Q was below the median in 312 of 383 (82%) cases, compared with only 51% of cases with high gradient severe AS (p < 0.001) (**Figure 1**).

Q was lower overall in women versus men (225.9 ± 45.8 ml/s vs. 255.3 ± 52.7 ml/s; p < 0.001). In women, Q was below the median in 65% of cases, compared with in only 40% of men (p < 0.001) (**Figure 2**). Women also had smaller ventricular dimensions (40.4 ± 5.7 mm vs. 45.6 ± 6.0 mm; p < 0.001).

FIGURE 1 Relationship Between Aortic Stenosis Subgroups and Flow Rate



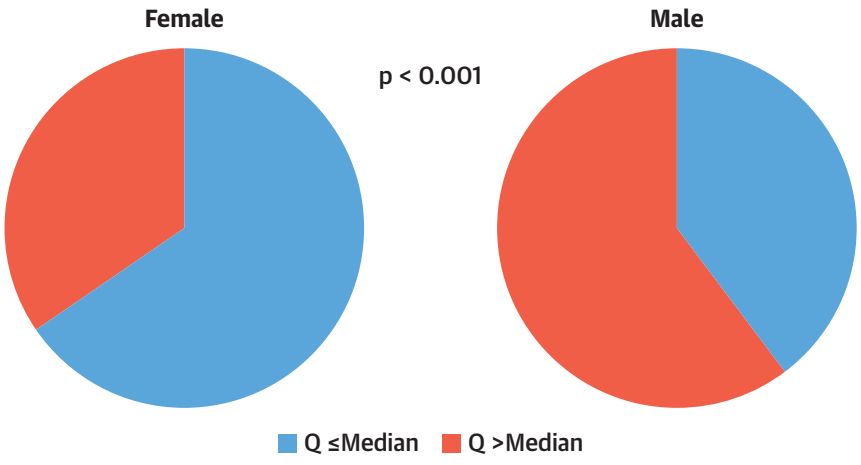
(A) Subgroups of AS by flow rate; **(B)** flow rates in high-gradient versus low-gradient severe AS. A total of 101 of 197 (51%) of high-gradient severe AS had Q ≤ median, and 312 of 383 (82%) of low-gradient AS had Q ≤ median (≤242 ml/s). Sev AS HG: n = 197; Mod AS LG: n = 536; Sev AS LG: n = 383; Mod AS HG: n = 15. AS = aortic stenosis; HG = high gradient; LG = low gradient; Mod = moderate; Q = transvalvular flow rate; Sev = severe.

Median follow-up time was 3.9 years (maximum 7.3 years). There were 395 of 1,131 (34.9%) deaths in follow-up, with a median time to death of 1.9 years. Patients with Q below the median had worse survival than those with Q above the median (**Figure 3**). Median time to SAVR/TAVR was 0.8 years. Rates of mortality and aortic valve replacement by subgroup of Q are reported in **Table 2**.

Q determined the prognostic value of AVA. If AVA was measured below the median Q, AVA ≤1.0 cm^2 was not prognostic for mortality (hazard ratio [HR]: 1.25; 95% confidence interval [CI]: 0.92 to 1.68; p = 0.15). In contrast, if AVA was measured at a Q above the median, AVA ≤1.0 cm^2 was highly prognostic for mortality (HR: 1.66; 95% CI: 1.19 to 2.33; p = 0.003) (**Table 3**). These findings were irrespective of age, sex, and valve replacement with SAVR or TAVR (as time-dependent covariates). Findings persisted after further multivariable adjustment for potential confounder variables (comorbidity, medication, and echocardiographic), which were significantly different at baseline between patients with Qs above or below the median (**Table 4**).

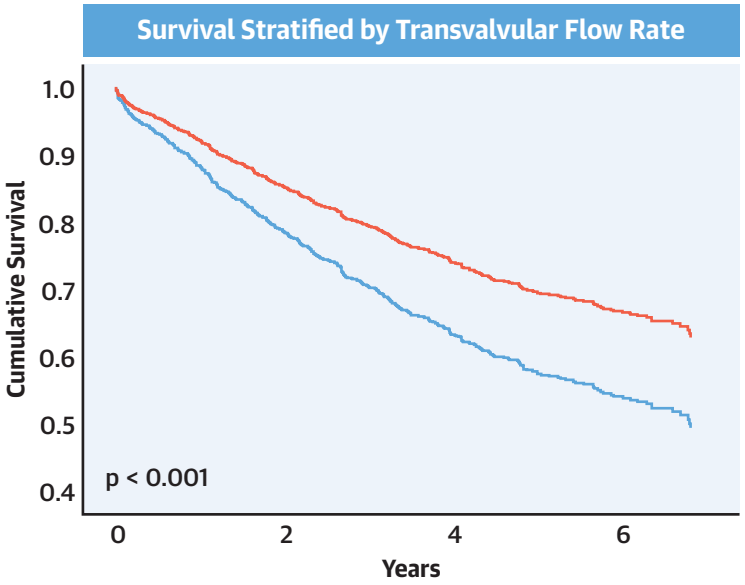
Interaction testing confirmed the effect of Q on AVA's prognostic value (Supplemental Table 1). With AVA and Q binarized (≤1.0/>1.0 cm^2

FIGURE 2 Flow Rate by Sex



In total, 297 of 454 (65%) female patients had Q ≤ median (≤242 ml/s) and 269 of 677 (40%) of male patients had Q ≤ median.
Q = transvalvular flow rate.

FIGURE 3 Survival in Aortic Stenosis Stratified By Resting Transvalvular Flow Rate



Number at risk

Years	0	1	2	3	4	5	6	7
Q ≤Median	566	492	429	344	270	182	120	19
Q >Median	565	527	465	367	277	207	131	20

Patients with flow rate below the median (≤242 ml/s) had worse overall survival than patients with flow rate above the median.
Q = transvalvular flow rate.

TABLE 2 Mortality Rate and Intervention Rate by Flow Rate

	Below Median Q (n = 566)	Above Median Q (n = 565)	Sig.
Death	232/566 (41)	163/565 (29)	<0.001
Aortic valve replacement (SAVR or TAVR)	166/566 (29)	188/565 (33)	NS

Values are n/N (%). Median Q 242 ml/s. Significance testing by chi-square test.
Q = transvalvular flow rate; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

TABLE 3 Prognostic Value of AVA ≤1.0 cm² by Flow Rate

	Hazard Ratio for Death* of AVA ≤1.0 cm²	95% CI for HR	Sig.
Below median Q	1.25	0.92-1.68	NS (0.15)
Above median Q	1.66	1.19-2.33	0.003

Median Q 242 ml/s. *Cox proportional hazards model for time to death (all-cause mortality), adjusted for age, sex, and surgical or transcatheter aortic valve replacement (as time-dependent covariates).
AVA = aortic valve area; Q = transvalvular flow rate.

and ≤ median / > median, respectively), the interaction of the 2 variables was significant for prediction of mortality. With AVA and Q as continuous variables, interaction testing confirmed the confounding effect of low Q on AVA's prognostic value seen in earlier hazard models.

Sensitivity analysis was performed by reducing the threshold value by 10 ml/s increments to find the lowest Q cutoff above which prognostic value of AVA was maintained (Supplemental Table 2). Prognostic value was significant above a cutoff of 242 ml/s (median) through 210 ml/s. We used 210 ml/s as the optimal cutoff.

VALIDATION COHORT. Baseline characteristics of the validation cohort are described in Supplemental Table 3 with a comparison to the primary cohort. The majority (84%) of patients had EF ≥50%. Mean and median Q in the validation cohort (216.8 ± 53.0 ml/s and 211.7 ml/s, respectively) were lower than in the primary cohort ($p < 0.001$).

The linear regression between the derived and measured Q closely approximated a line of identity providing strong validation of our Q derivation method (Supplemental Figure 3).

Follow-up time was longer in the validation cohort (median follow-up time 5.8 years, maximum follow-up 13.5 years) than in the primary cohort. There were 482 of 939 (51.3%) deaths and 542 of 939 (57.7%) SAVRs or TAVRs in the validation cohort. Median time to death was 3.8 years. Median time to SAVR/TAVR was 0.6 years. As was the case in the primary cohort, AVA ≤1.0 cm² was not independently predictive of mortality at Q below the median, whereas at Q above the median, AVA ≤1.0 cm² was independently predictive of mortality (Supplemental Table 4).

Q provided unique information to SVi about classification of flow state. Q was below the median in 205 of 619 (33.1%) patients with conventionally defined "normal flow" (SVi ≥35 ml/m²) (Figure 4). In patients from the validation cohort with normal SVi (≥35 ml/m²) (n = 619), where AVA would traditionally be considered to have good predictive value for outcomes, AVA ≤1.0 cm² was only prognostic for mortality when Q was above the median (HR: 1.65; 95% CI: 1.19 to 2.28; $p = 0.003$). That is, despite a normal SVi, AVA ≤1.0 cm² was not prognostic for mortality when Q was below the median (HR: 1.28; 95% CI: 0.85 to 1.92; $p = 0.24$) (Table 5). Additionally, in patients with normal SVi, patients with Q below the median had worse survival overall compared with patients with Q above the median (HR: 1.40; 95% CI: 1.10 to 1.79; $p = 0.006$) (Figure 5). ET was significantly longer in patients with low Q and normal SVi compared with patients with low Q and low SVi (337.5 ± 31.8 ms vs. 304.7 ± 34.0 ms; $p < 0.001$). When prognostic value of AVA was compared by SVi criteria (<35 and ≥35 ml/m²), SVi was not able to discriminate the prognostic value of AVA until Q was incorporated as a covariate (Supplemental Table 5). Receiver-operating characteristics of Q and SVi are described in Supplemental Table 6.

DISCUSSION

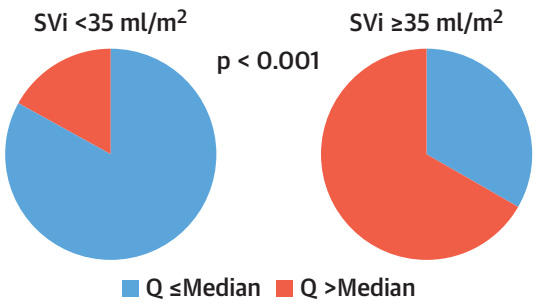
AVA HAS POOR PROGNOSTIC VALUE AT LOW TRANSVALVULAR FLOW RATE. The main finding of this study is that the prognostic value of AVA is dependent upon the transvalvular flow rate at the time of AVA measurement. This was observed and validated using 2 large, longitudinal cohorts from

TABLE 4 Prognostic Value of AVA ≤1.0 cm² by Flow Rate After Additional Multivariable Adjustment for Comorbidity, Medication, and Echocardiography Variables

	Hazard Ratio for Death* of AVA ≤1.0 cm²	95% CI for HR	Sig.
Below median Q	1.06	0.70-1.60	NS (0.80)
Above median Q	2.49	1.41-4.37	0.002

Median Q 242 ml/s. *Cox proportional hazards model for time to death (all-cause mortality), adjusted for age, sex, surgical or transcatheter aortic valve replacement (as time-dependent covariates), baseline diagnosis of heart failure, coronary artery disease, atrial fibrillation, chronic kidney disease, use of beta-blocker or oral anticoagulant, body surface area, absolute transvalvular flow rate, bicuspid valve status, mean aortic valve gradient, peak aortic valve gradient, left ventricular internal dimension at end-diastole, left ventricular ejection fraction, aortic sinus diameter, ascending aorta diameter, interventricular septal thickness, left ventricular outflow tract diameter, and left ventricular outflow tract velocity. Overall result pattern unchanged after removal of peak gradient from the model (due to collinearity with mean gradient) or if model run as backward stepwise regression.
Abbreviations as in Table 3.

FIGURE 4 Stroke Volume Versus Flow Rate Classification of Flow State



Although 265 of 320 (82.8%) patients with low SVi had flow rate below median (≤212 ml/s), 205 of 619 (33.1%) patients with normal SVi also had flow rate below median in the validation cohort. Q = transvalvular flow rate; SVi = stroke volume index.

different institutions. Our data suggest that current guideline recommendations about severity classification based on low AVA cannot be uniformly applied among AS patients. Specifically, based on poor prognostic information of AVA at low Q, our findings raise concerns about the validity of diagnoses of severe AS (using AVA) made at low Q. This is a novel finding with potential to widely affect clinical care of patients with aortic stenosis.

The mechanistic explanation for our findings is based on fundamental principles of material physics and fluid dynamics (8). The opening of a semi-compliant orifice (stenotic aortic valve) is dependent upon the valve compliance characteristics (severity of stenosis) and the transvalvular flow rate (volume per unit time). At low Q, the valve opening may be insufficient to produce the maximal effective orifice area or "true AVA." We have shown that this phenomenon clinically translates to a poor prognostic value of low AVA, if AVA was measured at low Q.

Our observations are mechanistically supported by studies showing change in AVA with change in Q. In an in vitro model, Voelker et al. (9) showed that changing Q from 100 to 200 ml/s changed measured AVA by 24%, whereas there was minimal change in AVA by changing Q from 200 to 300 ml/s. Rask et al. (10) showed that Q significantly altered AVA measurement by continuity equation. They showed that the percentage change in AVA was roughly one-half (0.56) the percentage change in Q, such that a 50% change in Q (e.g., from 160 to 240 ml/s) could alter AVA by 25%.

Our findings are also supported by other studies that have evaluated AS severity classification at different Q in patients with impaired ejection fraction receiving dobutamine infusion. Blais et al. (11) showed that classification of AS by AVA criteria was optimized only if the AVA was extrapolated to a "projected AVA" at a Q of 250 ml/s. Chahal et al. (12) showed that classification of AS by AVA criteria in patients with impaired EF was largely sufficient on a resting echocardiogram, without needing dobutamine infusion if resting Q was ≥200 ml/s, but dobutamine was needed to reclassify patients if resting Q was <200 ml/s. Although these studies looked at classification of AS based on agreement of AVA with other echocardiographic metrics at varying Q, our study, to the best of our knowledge, is the first to evaluate the effect of Q on the prognostic value of AVA for a clinical outcome in longitudinal data. We additionally included patients with normal EF.

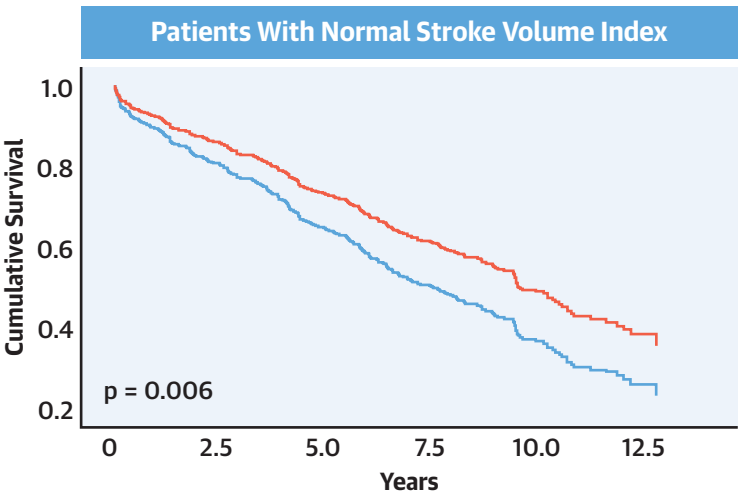
The findings of our study, and those of the previously mentioned studies, suggest that Q should be incorporated into the AS diagnostic and severity classification algorithm. The measurements required to determine Q are readily available in a standard echocardiographic study, and Q calculation could also be automated using routinely reported metrics (AVA, peak velocity, mean gradient) and our derivation method[illegible] 3). Specifically, in the presence of low Q and discordant metrics of severity (low AVA and low mean gradient), AVA should be recalculated above the threshold flow conditions necessary to determine the "true AVA" (**Central Illustration**). Whereas current methods use dobutamine to augment stroke volume or Q in patients with *impaired* EF, we propose that simple bedside maneuvers could be used to augment Q as part of a standard echocardiographic workflow, even in patients with *normal* EF. Studies have shown that left ventricular ET can be shortened with hand squeeze exercise (13,14). In a small supplementary study (details in Supplemental Appendix), we have verified this by showing that Q could be significantly augmented after only 30 s of hand-squeeze exercise, due to shortening of ET rather than increase in stroke volume (Supplemental Figure 5). However, this

TABLE 5 Prognostic Value of AVA ≤1.0 cm² According to Transvalvular Flow Rate in Patients With Normal Stroke Volume Index ≥35 ml/m²

	Hazard Ratio for Death* of AVA ≤1.0 cm²	95% CI for HR	Sig.
Below median Q	1.28	0.85-1.92	NS (0.24)
Above median Q	1.65	1.19-2.28	0.003

Median Q 212 ml/s. *Cox proportional hazards model for time to death (all-cause mortality), adjusted for surgical or transcatheter aortic valve replacement (as time-dependent covariates).
Abbreviations as in Table 3.

FIGURE 5 Survival Stratified by Flow Rate in Patients With Normal Stroke Volume Index (≥35 ml/m²)



Number at risk

Years	0	1	2	3	4	5	6	7	8	9	10	11	12
Q ≤Median	205	169	150	138	126	108	93	79	57	38	24	11	6
Q >Median	414	355	334	311	292	263	234	201	161	103	70	52	34

Q ≤Median Q >Median

In the validation cohort, even in patients with normal stroke volume index, flow rate below the median (≤212 ml/s) was associated with worse overall than flow rate above the median. Q = transvalvular flow rate.

bedside technique requires further investigation. Other bedside approaches worthy of investigation might include leg raising or arm weights (15). Using nonechocardiographic modalities, such as computed tomography calcium score, could also help clarify aortic stenosis severity in subjects with low Q (3).

Our study did not limit findings to patients with impaired EF. We evaluated all moderate or severe AS patients, the overwhelming majority of whom had normal EF. This is clinically important because low-gradient AS with preserved EF ("paradoxical" low gradient) is a far more prevalent group than low-gradient AS with reduced EF, and is an area of diagnostic uncertainty in severe AS (7,16).

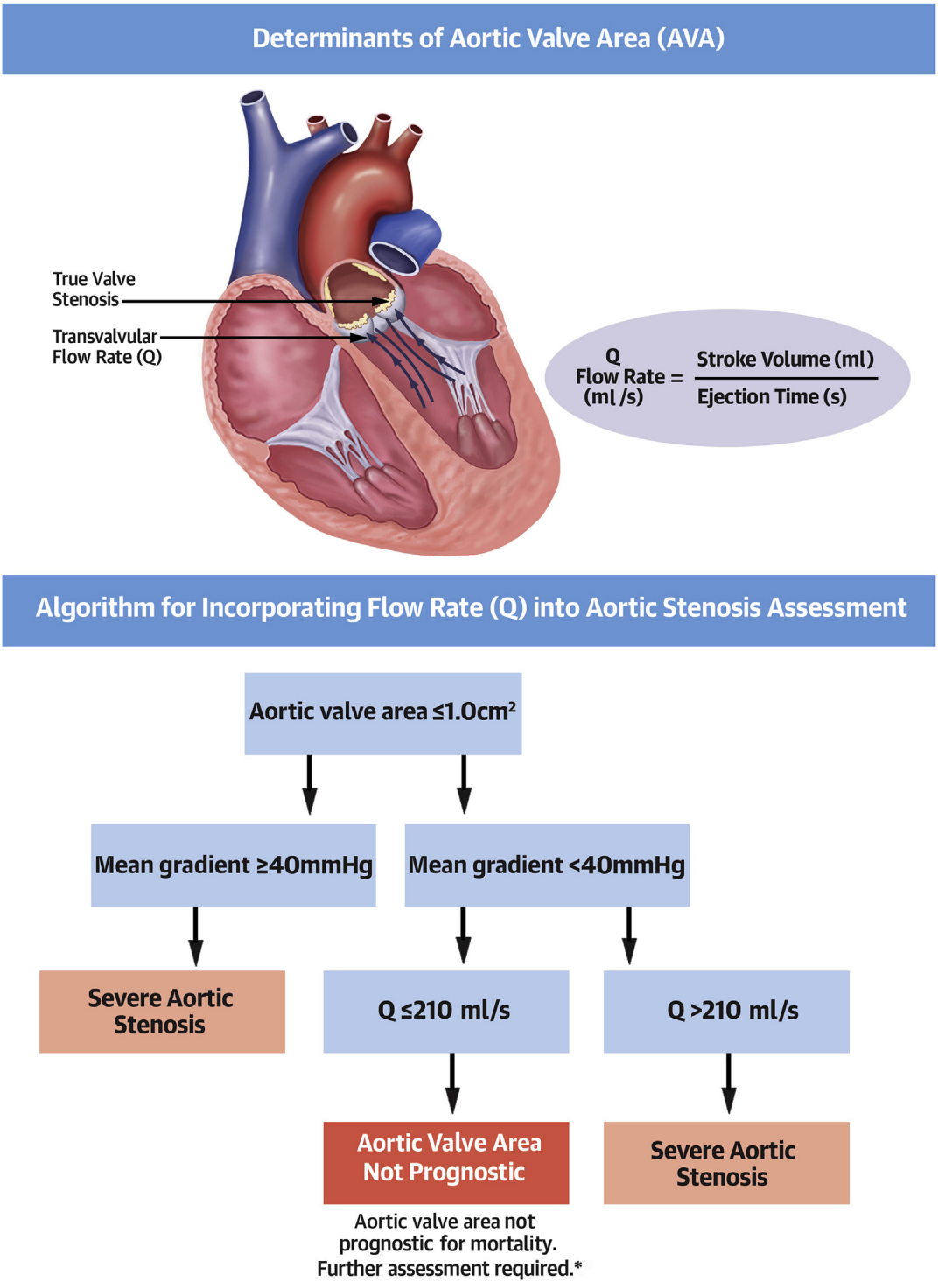
In addition to the novel finding of the impact of Q on prognostic value of AVA, we have confirmed the adverse prognostic impact of low Q itself in AS (**Figure 3**) (17,18).

LOW TRANSVALVULAR FLOW RATE EXPLAINS DISCORDANT SEVERITY METRICS IN AORTIC STENOSIS. Low Q provides a unifying mechanism of discordance between AVA and mean gradient in AS severity assessment. Because severe AS is defined and classified by both low AVA (≤1.0 cm²) and high mean gradient (≥40 mm Hg), our findings are particularly relevant in patients where low AVA is the only echocardiographic feature that meets criteria to define severe AS—namely, patients with low-gradient severe AS (AVA ≤1.0 cm² and mean gradient <40 mm Hg, i.e., "discordant severe AS"). Mean gradient is also dependent on Q; hence, at low Q, both AVA and mean gradient can be lower than they would be under normal flow conditions.

This phenomenon explains the predominance of discordant low-gradient severe AS in the below median Q group (**Figure 1**). Q was below the median in 82% (312 of 383) of patients with low-gradient severe AS diagnosis. Importantly, Q assessment can help clarify prognostic value of AVA in this situation of discordance, and therefore, can also help clarify true AS severity in discordant AS (**Central Illustration**).

TRANSVALVULAR FLOW RATE VERSUS STROKE VOLUME INDEX. The widespread awareness of the importance of flow state in AS commenced with appreciation of the importance of stroke volume (and SVi) in AS (7,16). These descriptions facilitated refined classification, diagnosis, prognosis, and therapeutic decision-making in AS. Notably, however, although

CENTRAL ILLUSTRATION **Algorithm for Incorporation of Flow Rate Into Assessment of Aortic Stenosis**



Namasivayam, M. et al. J Am Coll Cardiol. 2020;75(15):1758–69.

Aortic valve area measured at Q >210 ml/s is prognostic for mortality and is therefore valid as a marker of severe AS. *Further assessment when AVA is invalid may include augmentation of Q and/or use of alternative modalities, including computed tomography calcium score.

the term flow is commonly discussed in the AS published data, it is often a *volume* metric (stroke volume) that is actually being measured and referred to, whereas true flow itself (defined as volume per unit time) is rarely quantified. The primary aim of our study was not to compare prognostic value of SVi and Q, but rather to assess the impact of flow state on prognostic value of aortic valve area. In doing so, we sought to more accurately measure the flow state in AS by directly measuring the Q, defined by the mean volume of blood passing through the aortic valve per unit time during ventricular ejection (ratio of SV to ET). Recent work from the group of Senior et al. first highlighted the value in assessing flow state in AS by Q as an alternative to SVi (12,17,18). These studies have described both classification of AS by dobutamine echocardiography in patients with discordant low-gradient AS and low EF (12), but also the effect of flow rate on outcomes (17), even after intervention (18). We have sought to build upon this foundation by evaluating the effect of Q on *prognostic value of AVA* in AS, regardless of EF.

In our data, the classification of flow state by SVi and Q was different. Nearly one-third of patients with "normal flow" defined by SVi in fact had Q below the median (**Figure 4**). Moreover, Q assessment could also stratify prognosis beyond traditional SVi criteria. In patients with "normal flow" by SVi criteria, having a Q below the median was associated with worse survival (**Figure 5**). Most importantly, however, in this group with *normal* SVi, AVA ≤1.0 cm^2 was *not* prognostic for mortality if Q was below the median, but AVA ≤1.0 cm^2 was highly prognostic for mortality when Q was above the median (**Table 5**). Additionally, SVi could not independently discriminate the prognostic value of AVA until Q was considered (Supplemental Table 5). Thus, measurement of Q, which incorporates volume and time, adds not only to classification, but also prognostication in AS over and above the use of the current guideline standard (4), SVi. Volume and flow are not synonymous.

Prolongation of left ventricular ET is the mechanism of low flow rate *despite normal stroke volume*. This is because transvalvular flow rate is the ratio of SV to ET. Indeed, ET was significantly longer in patients with low Q and normal SVi compared with patients with low Q and low SVi (337.5 ± 31.8 ms vs. 304.7 ± 34.0 ms; $p < 0.001$). Prolongation of ET can occur not only due to valvular afterload, but also because of hypertension and age-related arterial stiffness (19,20), both common in AS ("valvulo-arterial load") (16). ET prolongation therefore provides insight into the heretofore perplexing but important clinical scenario of low-gradient severe AS in the setting of normal stroke volume (a condition currently termed "normal flow low gradient AS") (21). Indeed, recent work in a propensity-matched dataset has shown that the beneficial effect of aortic valve replacement might be better guided by Q rather than SVi (22). Vamvakidou et al. (18) also showed that low Q, and not low SVi, was prognostic for mortality in multivariable analysis in patients undergoing aortic valve intervention.

LOW TRANSVALVULAR FLOW RATE IS MORE COMMON IN WOMEN. Women more commonly have discordant metrics of severity, and hence, pose greater clinical challenges during AS assessment (23). We saw important sex differences in Q distribution that can explain this observation. Q was below the median in 65% of women, compared with 40% of men ($p < 0.001$) (**Figure 2**). Knowing Q at the time of AVA calculation is therefore particularly important in women with discordant severe AS.

STUDY LIMITATIONS. Although the retrospective nature of our analysis carries inherent limitations, the primary cohort consisted of patients who had dedicated longitudinal follow-up with complete outcome data. We believe that this type of analysis represents the most practical approach available to test our hypothesis in a large cohort. Importantly, our findings were validated in a separate, large longitudinal cohort of patients from a different center, mitigating some of the limitations of retrospective analysis. Indeed, using our approach, the optimal cutoff for prognostic threshold in the primary cohort was identical (rounded to the nearest 10 ml/s) to the median for the validation cohort. This preserved our key finding in both cohorts, such that at low Q (below 210 ml/s), AVA has poor prognostic value, but above 210 ml/s, AVA is prognostic. This is despite the fact that Q distribution was lower in the validation cohort compared with the primary cohort. Differences in Q distribution between cohorts may have resulted from the validation center being a recognized referral center for low-gradient AS, attracting a greater than average proportion of patients with low Q.

Although Q adds to the current diagnostic, prognostic, and classification framework of AS, it still requires left ventricular outflow tract (LVOT) diameter measurement in its derivation, and hence is subject to underestimation (along with AVA and SVi) if LVOT diameter is underestimated. Although LVOT diameter was lower in patients with Q below the median than in patients with Q above the median (**Table 1**), after adjustment for this potential confounder, our observations about the effect of Q on prognostic value of AVA were preserved (**Table 4**). Moreover, a low

AVA and low Q resulting from LVOT underestimation would not alter our overall clinical message urging caution in this very situation (**Central Illustration**). Future approaches might adopt 3-dimensional approaches that could obviate LVOT diameter measurement (24). In both the primary and validation cohorts, although the presence of atrial fibrillation as a comorbidity was known, it was not known which patients were in atrial fibrillation at the time of echocardiography—a potential measurement confounder. Atrial fibrillation was more common at low Q (**Table 1**); however, after multivariable adjustment for this (**Table 4**), the key findings of this study remained unchanged, which is reassuring.

CONCLUSIONS

Transvalvular flow rate alters the prognostic value of AVA in AS. AVA ≤1.0 cm^2 is independently prognostic for mortality at normal flow rates. In patients with low flow rates, AVA ≤1.0 cm^2 is not an independent predictor of mortality related to aortic stenosis and is therefore not a valid defining feature of severe aortic stenosis. Flow rate assessment should be incorporated into diagnosis, classification, and prognosis schema for aortic stenosis.

ADDRESS FOR CORRESPONDENCE: Dr. Judy Hung, Division of Cardiology, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114. E-mail: jhung@mgh.harvard.edu. Twitter: @JudyHungMD, @MayoNamasivayam.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with AS, transvalvular flow rate is an important determinant of the prognostic value of AVA. Low AVA measured at low flow rate does not reliably identify severe AS, while small valve orifice area measured at sufficient flow rate identifies patients who are at greater risk of mortality.

TRANSLATIONAL OUTLOOK: Prospective investigations are needed to clarify the diagnostic utility of measuring transvalvular flow rate in patients with AS.

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KEY WORDS aortic stenosis, flow rate, low flow, low gradient, outcome, prognosis

APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.