JACC STATE-OF-THE-ART REVIEW

Evaluating Medical Therapy for Calcific Aortic Stenosis

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ABSTRACT

Despite numerous promising therapeutic targets, there are no proven medical treatments for calcific aortic stenosis (AS). Multiple stakeholders need to come together and several scientific, operational, and trial design challenges must be addressed to capitalize on the recent and emerging mechanistic insights into this prevalent heart valve disease. This review briefly discusses the pathobiology and most promising pharmacologic targets, screening, diagnosis and progression of AS, identification of subgroups that should be targeted in clinical trials, and the need to elicit the patient voice earlier rather than later in clinical trial design and implementation. Potential trial end points and tools for assessment and approaches to implementation and design of clinical trials are reviewed. The efficiencies and advantages offered by a clinical trial network and platform trial approach are highlighted. The objective is to provide practical guidance that will facilitate a series of trials to identify effective medical therapies for AS resulting in expansion of therapeutic options to complement mechanical solutions for late-stage disease. (J Am Coll Cardiol 2021;78:2354–2376) © 2021 by the American College of Cardiology Foundation.

Calcific aortic valve stenosis is widely prevalent among adults >65 years of age; approximately 25% have aortic sclerosis, the pathological precursor to aortic stenosis (AS), which is observed in 5%-10% of adults this age (1-3). Given the strong relationship between aging and AS, it is anticipated that there will be a doubling in the prevalence of AS in the coming decades as life expectancy

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HIGHLIGHTS

- Despite numerous promising targets, no medical therapies for AS have proven effective.
- Better tools are needed to detect early-stage AS and to identify patients prone to rapid progression.
- A clinical trial network and platform trial could accelerate discovery of improved methods of surveillance and effective therapies.

increases and the population ages (4). The only known effective treatment for AS is aortic valve replacement (AVR), which improves survival and quality of life for patients who are symptomatic with severe AS; approximately 150,000 surgical or transcatheter AVRs are performed annually in the United States (5,6). Worldwide, AS is responsible for ~125,000 deaths and ~350,000 AVRs with an associated loss of 1.8 million disability-adjusted life years per year (7). The high residual risk related to heart failure even after successful AVR in conjunction with low procedural complication rates and low morbidity from transcatheter AVR have motivated studies to test whether earlier AVR before symptom onset or with less severe stenosis might yield better outcomes (8-10). Although these strategy trials may lead to important improvements in patient outcomes, they remain limited in their impact because they reinforce the long-standing paradigm that AS is simply a mechanical disease treated with a mechanical solution.

Ongoing research has led to significant progress in elucidating the pathobiology of AS and in identifying promising therapeutic targets. However, there are currently no recommended medical therapies and a dearth of actively enrolling clinical trials caused by several barriers (11). Medical therapies targeting both the *valve* (to slow/halt progressive valve obstruction) and the *ventricle* (to prevent/reverse maladaptive cardiac remodeling and dysfunction) are needed to delay or avoid the development of heart failure and the need for AVR.

Given that valve obstruction is the primary stimulus for cardiac remodeling that occurs in response to pressure overload, this review focuses principally on medical therapies that target the pathobiology underlying progressive disease in the valve leaflets. Our overarching objective is to provide a roadmap for efficiently testing promising medical therapies to

slow AS progression. We hope that this practical guidance will facilitate a series of trials to identify effective medical therapies for treatment of AS, resulting in expansion of therapeutic options to complement mechanical solutions for late-stage disease.

PATHOBIOLOGY AND PROMISING THERAPEUTIC TARGETS FOR AS

PATHOBIOLOGY OF AS. A detailed description of the pathobiology of AS and discussion of promising therapeutic targets are beyond the scope of this review but have been reviewed elsewhere (11-15). The pathophysiology of AS appears to have 2 phases. The earlier initiation phase demonstrates many similarities with atherosclerosis, with accumulation of apolipoprotein (apo) B–containing lipoproteins in the subendothelium, lipoprotein oxidation, activation of inflammatory pathways, production of angiotensin-converting enzyme, up-regulation of adhesion molecules and matrix metalloproteinases, and shear stress. Consequently, risk factors for the incidence of AS are also similar and include older age, dyslipidemia, high lipoprotein(a) (Lp[a]) levels, hypertension, smoking, obesity, as well as bicuspid morphology.

In contrast, the later stages of AS result in progressive leaflet fibrosis and calcification and are dominated by alterations in complex, inter-related cellular and molecular pathways and perturbations in mineral metabolism. Together these drive increased leaflet thickening and valve stiffness that lead to progressive AS. Disease progression in this propagation phase is most closely linked to markers of valve calcification and valve stenosis severity (5,15,16). The molecular mechanisms involved in both the initiation and propagation phases of AS, as well as the gene candidates identified through genetic association studies, suggest potential therapeutic targets for AS prevention and treatment that may be phase-specific (**Figure 1**) (13,17-19).

Although the focus of this manuscript is on *valvular* pathology, the functional consequences of AS on the myocardium are also important. Increased afterload caused by valve obstruction induces a hypertrophic response in the left ventricle that restores wall stress and maintains cardiac performance for many years if not decades. Eventually this process decompensates, with progressive myocyte cell death and myocardial fibrosis driving the transition to heart failure, symptom development, and adverse events (20).

FIGURE 1 Disease Progression in CAS

A Anatomical Progression of Calcific Aortic Stenosis

Normal Aortic Valve · Aortic Sclerosis · Mild-Moderate Stenosis · Severe Stenosis

B Pathophysiology of Calcific Aortic Stenosis

Initiation Phase
Genetic variants
Mechanical stress
Valve morphology
Inflammation
Dyslipidemia (LDL-c, Lp(a))

Propagation Phase
VIC activation
Osteoblast differentiation
Fibrosis
Calcification

C Therapeutic Targets for Calcific Aortic Stenosis

Targeting lipid infiltration
PCSK9i, LPAi,
DPP4i and TZDs

Targeting Notch1-CDH11 axis
microRNA-34a, H19 and CDH11

Targeting fibro-calcific response
RAAS inhibitors, Vitamin K, PALMD,
Inositol phosphate analogs,
upregulating NO-cGMP signaling

PROMISING THERAPEUTIC TARGETS FOR CALCIFIC AS.

Lipid-lowering therapy. Despite the failure of statin therapy to influence AS progression (21,22), hypothesis-driven and hypothesis-free genetic association studies confirmed the role of apo B-containing atherogenic lipoprotein particles as being involved in the earliest steps of aortic valve micro and macro calcification (the initiation phase) (23-26). These include very-low-density, intermediate-density, and low-density lipoprotein particles, as well as Lp(a). Reduction of apo B-containing lipoprotein particles may exert beneficial effects in AS through the inhibition of leaflet mineralization, the inhibition of macrophage infiltration, the prevention of osteoblast-like phenotype transformation, and the reduction of leaflet cholesterol accumulation. Importantly, patients with elevated Lp(a) levels also demonstrate faster disease progression, suggesting an effect on the propagation as well as initiation phases of the disease (27). PCSK9 and Lp(a) inhibitors have been shown to provide unprecedented reductions in non-Lp(a) and Lp(a)-containing lipoprotein particles, respectively, and may be key in the prevention of AS if adequately tested in randomized controlled trials (RCTs) of patients deemed high-risk (28,29).

Renin-angiotensin-aldosterone system. The effects of the renin-angiotensin-aldosterone system inhibitors in patients with AS on surrogate endpoints in small studies have been described elsewhere (12). Beyond their blood pressure effects, renin-angiotensin-aldosterone system inhibition might reduce pro-fibrotic processes within the valve leaflets and myocardium in patients with AS, thereby potentially slowing valve narrowing and preventing/reversing maladaptive cardiac remodeling (12). The ARBAS (Angiotensin Receptor Blockers in Aortic Stenosis; NCT04913870) RCT will investigate whether ARBs can slow disease progression in the valve and delay fibrosis accumulation in the myocardium.

Metabolic targets. Drugs targeting glucose-insulin homeostasis such as DPP4 inhibitors and thiazolidinediones also represent potential therapies for AS. DPP4 has many biological functions including a possible role in a wide range of heart diseases. Endothelial dysfunction in the aortic valve may lead to higher expression of DPP4, which in turn, may promote osteogenic mechanisms in aortic valves (30). The beneficial impact of thiazolidinediones in the aortic valve may be caused by the ability of these compounds to reduce the expression of the receptor for advanced glycation end products, thereby exerting anti-inflammatory effects. However, the level of evidence for hypoglycemic drugs is currently only supported by retrospective and/or preclinical studies with RCTs awaited (31,32).

Nitric oxide cyclic guanosine monophosphate signaling. Preclinical studies have demonstrated the role of phosphodiesterase type 5 inhibition in preventing and reversing maladaptive cardiac remodeling and dysfunction in the setting of pressure overload (33,34). In a small clinical study, administration of sildenafil was associated with acute improvements in pulmonary and systemic hemodynamics and biventricular unloading in patients with severe AS, but longer term studies are needed to assess effects on cardiac remodeling (35).

FIGURE 1 Continued

(A) Anatomical progression of calcific aortic stenosis (CAS) with valve anatomy viewed from the aortic side and open in systole. **(B)** Corresponding clinically relevant risk factors and histological development of CAS. Early lesion initiation is caused by lipid infiltration into the subendothelium (LPA, FADS1/2). Infiltration initiation is caused by mechanical stress, dyslipidemia or abnormal valve morphology. Lipoprotein(a) (Lp[a]), low-density lipoprotein (LDL), oxidized low-density lipoprotein (OxLDL), and oxidized phospholipids (OxPLs) enter into the subendothelial space triggering the recruitment, activation, and proliferation of monocytes and macrophages. At the molecular level, the calcification process driven by the OxPL content of OxLDLs leads to the enzymatic generation of lysophosphatidic acid (LysoPA) via autotaxin (ATX). In turn, LysoPA promotes osteogenic transition though the production of BMP2, which associates, with the expression of bone-related transcription factors such as RUNX2 and MSX2. In addition, activation of macrophages in aortic valve by OxLDL promotes the production of tumor necrosis factor α (TNFα) and interleukin 1β (IL1β) with pro-osteogenic properties. Chymase and angiotensin-converting enzyme (ACE) promote the production of angiotensin II, which increases the synthesis and secretion of collagen by valve interstitial cell (VICs). This leads to an imbalance in metalloproteinase synthesis/inhibition pathway fibrous tissue begins to accumulate in the aortic valve. Early in the disease progression VICs and macrophages secret microvesicles initiating microcalcification. Overexpression of the ectonucleotidase ENPP1 and alkaline phosphatase (ALP) further increases osteogenic mineralization. **(Inset)** Regulation of Notch1 transcription. H19 suppresses transcription of Notch1 by blocking the binding of p53 to the Notch1 promoter. The microRNA miR-34a is able to bind directly to the Notch1 transcript resulting in decreased translation of Notch1 messenger RNA. Both pathways of Notch1 suppression result in an increase CDH11 expression and calcification of the aortic valve. **(C)** Therapeutic modalities currently under investigation for CAS. AMP = adenosine monophosphate; ATP = adenosine triphosphate; DPP4i = DPP4 inhibitor; LDL-c = low-density lipoprotein cholesterol; LPAi = LPA inhibitor; Lp-PLA₂ = lipoprotein-associated phospholipase A₂; NO-cGMP = nitric oxide cyclic guanosine monophosphate; PCSK9i = PCSK9 inhibitor; RAAS = renin-angiotensin-aldosterone system; RANKL = receptor activator of nuclear factor kappa-B ligand; sPLA₂ = secretory phospholipase A₂; TZD = thiazolidinedione.

TABLE 1 Prospective Studies Evaluating Progression of AS Severity Over Time

First Author (Ref. #)	Year	N	Mean Follow-Up When Available (y)	Baseline Population Entry Criteria and Study Design	Modality to Assess Progression	Baseline Aortic Valve Measurements (and % With Mild, Moderate, and Severe When Available)	Annualized Progression Rate of AS Severity (AVA, V_{peak}, ΔP, AVC Score)
Otto et al (70)	1989	42	1.7	Echocardiographic evidence of AS (including patients who are symptomatic and ones that are asymptomatic) $V_{peak} \geq 2.6$ m/s	Echocardiography	V_{peak}: 3.7 m/s ΔP_{mean}: 35 mm Hg	AVA: −0.1 cm²/y V_{peak}: 0.36 ± 0.31 m/s/y ΔP_{mean}: 8 (−7 to 23) mm Hg/y
Faggiano et al (71)	1992	45	1.5	Physical exam and echocardiographic evidence of AS $V_{peak} \geq 2.5$ m/s	Echocardiography	AVA: 0.75 ± 0.3 cm² V_{peak}: 4.0 ± 0.7 m/s ΔP_{max}: 64 ± 30 mm Hg Moderate (AVA): 16% Severe (AVA): 84%	AVA: −0.1 ± 0.13 cm²/y V_{peak}: 0.4 ± 0.3 m/s/y ΔP_{max}: 15 ± 10 mm Hg/y
Peter et al (72)	1993	49	2.7	Physical exam findings of AS and initial peak pressure gradient ≥16 mm Hg on echocardiography	Echocardiography	ΔP_{max}: 38 ± 15 mm Hg	ΔP_{max}: 11 ± 11 mm Hg/y
Otto et al (73)	1997	123	2.5	Asymptomatic, physical exam, and echocardiographic evidence of AS $V_{peak} \geq 2.5$ m/s	Echocardiography	AVA: 1.3 ± 0.5 cm² V_{peak}: 3.6 ± 0.6 m/s ΔP_{mean}: 29 ± 11 mm Hg	AVA: −0.12 ± 0.19 cm²/y V_{peak}: 0.32 ± 0.34 m/s/y ΔP_{mean}: 7 ± 7 mm Hg/y
Cowell et al (74)	2005	155	2.1[a]	Echocardiographic evidence of calcific AS ($V_{peak} \geq 2.5$ m/s) RCT (SALTIRE)	Echocardiography and CT	Placebo: AVA: 1.02 ± 0.41 cm² V_{peak}: 3.45 ± 0.67 m/s ΔP_{peak}: 49.5 ± 19.5 mm Hg AVC: 6,621 (3,037-9,575) AU Statin: AVA: 1.03 ± 0.4 cm² V_{peak}: 3.39 ± 0.62 m/s ΔP_{peak}: 47.8 ± 17.4 AVC: 5,424 (2,750-9,689) AU	All patients: AVA: −0.081 ± 0.107 cm²/y V_{peak}: 0.201 ± 0.208 m/s/y ΔP_{peak}: 6.52 ± 7.24 mm Hg/y AVC: 1,608 ± 1,865 AU/y Placebo: AVA: −0.083 ± 0.107 cm²/y V_{peak}: 0.203 ± 0.208 m/s/y ΔP_{peak}: 6.56 ± 7.10 mm Hg/y AVC: 1,648 ± 1,790 AU/y Statin: AVA: −0.079 ± 0.107 cm²/y V_{peak}: 0.199 ± 0.210 m/s/y ΔP_{peak}: 6.48 ± 7.43 mm Hg/y AVC: 1,564 ± 1 956 AU/y
Rossebo et al (22)	2008	1873	4.4[a]	Echocardiographic evidence of mild to moderate AS (V_{peak} 2.5-4 m/s) without symptoms RCT (SEAS)	Echocardiography	Placebo: AVA: 1.27 ± 0.46 cm² V_{peak}: 3.10 ± 0.54 m/s ΔP_{mean}: 23.0 ± 8.7 mm Hg Statin/ezetimibe: AVA: 1.29 ± 0.48 cm² V_{peak}: 3.09 ± 0.55 m/s ΔP_{mean}: 22.7 ± 8.8 mm Hg	Placebo: AVA: −0.03 ± 0.1 cm²/y V_{peak}: 0.16 ± 0.01 m/s/y ΔP_{mean}: 2.8 ± 0.1 mm Hg/y Statin/ezetimibe: AVA: −0.03 ± 0.1 cm²/y V_{peak}: 0.15 ± 0.01 m/s/y ΔP_{mean}: 2.7 ± 0.1 mm Hg/y
Chan et al (21)	2010	269	3.5[a]	Echocardiographic evidence of mild to moderate AS (V_{peak} 2.5-4.0 m/s) without symptoms RCT (ASTRONOMER)	Echocardiography	Placebo: AVA: 1.56 ± 0.70 cm² V_{peak}: 3.19 ± 0.42 m/s ΔP_{mean}: 23.1 ± 7.6 mm Hg Statin: AVA: 1.49 ± 0.71 cm² V_{peak}: 3.16 ± 0.42 m/s ΔP_{mean}: 22.5 ± 7.6 mm Hg	Placebo: AVA: −0.08 ± 0.21 cm²/y ΔP_{mean}: 3.9 ± 4.9 mm Hg/y Statin: AVA: −0.07 ± 0.15 cm²/y ΔP_{mean}: 3.8 ± 4.4 mm Hg/y
Hekimian et al (75)	2013	110	1	Echocardiographic evidence of at least mild AS ($\Delta P_{mean} \geq 10$ mm Hg and aortic valve structural changes consistent with AS) without symptoms, and enrolled in the COFRASA study. Echocardiography follow-up completed at 1 y	Echocardiography	V_{peak}: 3.07 ± 0.82 m/s ΔP_{mean}: 24 ± 16 mm Hg	V_{peak}: 0.21 ± 0.30 m/s/y ΔP_{mean}: 4 ± 6 mm Hg/y

Continued on the next page

TABLE 1 Continued

First Author (Ref. #)	Year	N	Mean Follow-Up When Available (y)	Baseline Population Entry Criteria and Study Design	Modality to Assess Progression	Baseline Aortic Valve Measurements (and % With Mild, Moderate, and Severe When Available)	Annualized Progression Rate of AS Severity (AVA, V_{peak}, ΔP, AVC Score)
Kearney et al	2013	239 (147 included in progression analysis)	6.5	Patients treated at a single Australian tertiary university with baseline AS (ΔP_{mean} >10 mm Hg); patients with at least 2 echocardiograms >6 months apart were included in progression analysis	Echocardiography	Progression analysis cohort: ΔP_{mean}: 21 ± 11 mm Hg Mild: 67% Moderate: 23% Severe: 10%	Progression analysis cohort: AVA: −0.11 ± 0.20 cm²/y ΔP_{mean}: 5.0 ± 5.2 mm Hg/y Mild: AVA: −0.16 ± 0.20 cm²/y ΔP_{mean}: 3.7 ± 4.0 mm Hg/y Moderate: AVA: −0.11 ± 0.21 cm²/y ΔP_{mean}: 6.4 ± 5.1 mm Hg/y Severe: AVA: −0.02 ± 0.12 cm²/y ΔP_{mean}: 10.2 ± 7.7 mm Hg/y
Capoulade et al (76)	2015	183	2.5	Echocardiographic evidence of at least mild AS (V_{peak} >2 m/s), without symptoms, enrolled in the PROGRESSA study with 1-y follow-up and laboratory data ($Lp\text{-}PLA_2$) available	Echocardiography	AVA: 1.26 ± 0.29 cm² V_{peak}: 2.80 ± 0.60 m/s ΔP_{mean}: 19.0 ± 9.0 mm Hg Mild (V_{peak}): <3.0 m/s: 29% Moderate (V_{peak}): 3.0 to 3.9 m/s: 29% Severe (V_{peak}): ≥4.0 m/s: 4%	All patients: V_{peak} ($Lp\text{-}PLA_2$ <11.4): 0.12 ± 0.02 m/s/y V_{peak} ($Lp\text{-}PLA_2$ >11.4): 0.17 ± 0.03 m/s/y Mild: V_{peak} ($Lp\text{-}PLA_2$ <11.4): 0.09 ± 0.02 m/s/y V_{peak} ($Lp\text{-}PLA_2$ >11.4): 0.16 ± 0.02 m/s/y Moderate to severe: V_{peak} ($Lp\text{-}PLA_2$ <11.4): 0.19 ± 0.04 m/s/y V_{peak} ($Lp\text{-}PLA_2$ >11.4): 0.20 ± 0.06 m/s/y
Nguyen et al (77)	2016	203	3.2	Echocardiographic evidence of at least mild AS without symptoms, enrolled in COFRASA/GENERAC, with echocardiography and CT at baseline (and yearly thereafter) and at least 2-y follow-up	Echocardiography and CT	AVA: 1.39 ± 0.37 cm² V_{peak}: 3.03 ± 0.65 m/s ΔP_{mean}: 23 ± 11 mm Hg AVC: 1,168 ± 984 AU Mild: 47% Moderate: 44% Severe: 9%	AVA: −0.08 ± 0.07 cm²/y V_{peak}: 0.17 ± 0.16 m/s/y ΔP_{mean}: 3 ± 4 mm Hg/y AVC: 218 ± 226 AU/y
Tastet et al (94)	2017	101	2	Echocardiographic evidence of at least mild AS (V_{peak} >2 m/s), without symptoms, enrolled in the PROGRESSA study, and with follow-up CT at 2 y	Echocardiography and CT	No systolic hypertension: V_{peak}: 2.8 ± 0.5 m/s ΔP_{mean}: 18 ± 7 mm Hg AVC: 595 (339, 1,212) AU Systolic hypertension: V_{peak}: 2.8 ± 0.4 m/s ΔP_{mean}: 17 ± 7 mm Hg AVC: 665 (406, 1,096) AU	No systolic hypertension: AVC: 78.5 (29, 151.5) AU/y Systolic hypertension: AVC: 185 (63, 412) AU/y
Tastet et al (78)	2017	323	2.3	Echocardiographic evidence of AS with echocardiography and MDCT within 3 months and second echocardiographic exam within ≥6 months	Echocardiography and CT	Women: ΔP_{mean}: 24 ± 13 AVC: 531 (224, 1,098) Men: ΔP_{mean}: 22 ± 10 AVC: 1,019 (571, 1,921)	Women with nonsevere baseline AVC: ΔP_{mean}: 2.8 (0.5, 5.6) mm Hg/y Women with severe baseline AVC: ΔP_{mean}: 6.4 (3.4, 16.3) mm Hg/y Men with nonsevere baseline AVC: ΔP_{mean}: 2.0 (0.5, 4.6) mm Hg/y Men with severe baseline AVC: ΔP_{mean}: 5.6 (2.4, 8.8) mm Hg/y
Tastet et al (79)	2018	159	2	Echocardiographic evidence of at least mild AS (V_{peak} >2 m/s), without symptoms, enrolled in the PROGRESSA study, and with laboratory data (including apo B and apo A-I levels) and 2-year follow-up data available	Echocardiography	All patients: AVA: 1.25 ± 0.25 cm² V_{peak}: 2.7 ± 0.5 m/s ΔP_{mean}: 18 ± 8 mm Hg Apo B/apo A-I <0.62: AVA: 1.23 ± 0.26 cm² V_{peak}: 2.7 ± 0.4 m/s ΔP_{mean}: 17 ± 7 mm Hg Apo B/apo A-I ≥0.62: AVA: 1.28 ± 0.22 cm² V_{peak}: 2.8 ± 0.5 m/s ΔP_{mean}: 18 ± 9 mm Hg	Apo B/apo A-I <0.62: V_{peak}: 0.08 (0.005, 0.18) m/s Apo B/apo A-I ≥0.62: V_{peak}: 0.15 (0.0045, 0.245) m/s

TABLE 1 Continued

First Author (Ref. #)	Year	N	Mean Follow-Up When Available (y)	Baseline Population Entry Criteria and Study Design	Modality to Assess Progression	Baseline Aortic Valve Measurements (and % With Mild, Moderate, and Severe When Available)	Annualized Progression Rate of AS Severity (AVA, V_{peak}, ΔP, AVC Score)
Kubota et al (80)	2018	296	3	Echocardiographic evidence of at least mild AS (ΔP_{mean} ≥10 mm Hg and aortic valve structural changes consistent with AS) without symptoms, enrolled in COFRASA/GENERAC, with echocardiography and CT at baseline (and yearly thereafter) and at least 1-year follow-up	Echocardiography and CT	AVA: 1.4 ± 0.4 cm² V_{peak}: 3.13 ± 0.76 m/s ΔP_{mean}: 25 ± 16 mm Hg AVC: 1,339 ± 1,217 AU Mild: 44% Moderate: 43% Severe: 13%	AVA: −0.09 ± 0.09 cm²/y V_{peak}: 0.18 ± 0.18 m/s/y ΔP_{mean}: 4 ± 4 mm Hg/y AVC: 223 ± 301 AU/y
Tastet et al (81)	2019	303 (CT, N = 220)	2.6[a] (echocardiography) and 2[a] (CT)	Echocardiographic evidence of at least mild AS (V_{peak} ≥2.0 m/s and/or AVA <2.0 cm²) and with available repeat echocardiography or CT within >6 months Prospective and retrospective data collection	Echocardiography and CT	Warfarin: V_{peak}: 2.5 ± 0.5 m/s AVC: 395 (63, 991) AU DOAC: V_{peak}: 2.3 ± 0.5 m/s AVC: 322 (64, 820) AU No anticoagulation: V_{peak}: 2.7 ± 0.4 m/s AVC: 511 (254, 1,015) AU	Warfarin: V_{peak}: 0.14 (0.06, 0.32) m/s/y AVC: 204 (48, 317) AU/y DOAC: V_{peak}: 0.10 (−0.01, 0.20) m/s/y AVC: 66 (11, 86) AU/y No anticoagulation: V_{peak}: 0.09 (0.04, 0.19) m/s/y AVC: 94 (31, 203) AU/y
Doris et al (82)	2020	114 (reproducibility cohort, n = 33; progression cohort, n = 81)	2[a]	Evidence of AS (V_{peak} >2 m/s). Reproducibility cohort: repeat echocardiography or CT AVC scanning within 4 wk. Disease progression cohort: repeat echocardiography, CT, or both after at least 1 y	Echocardiography and CT	Disease progression cohort: AVA: 1.1 (0.9, 1.4) cm² V_{peak}: 3.4 (2.8, 4.1) m/s ΔP_{mean}: 25 (16, 36) mm Hg AVC: 1,339 (553, 2,422) Mild: 31% Moderate: 41% Severe: 28%	All patients: AVA: −0.1 (−0.2, 0.0) cm²/y V_{peak}: 0.1 (0.0, 0.3) m/s/y ΔP_{mean}: 2 (0, 4) mm Hg/y AVC: 152 (65, 375) AU/y Mild: AVA: −0.1 (−0.2, 0.0) cm²/y V_{peak}: 0.1 (0.0, 0.2) m/s/y ΔP_{mean}: 1 (0, 2) mm Hg/y AVC: 64 (48, 134) AU/y Moderate: AVA: −0.1 (−0.1, 0.0) cm²/y V_{peak}: 0.2 (0.1, 0.3) m/s/y ΔP_{mean}: 3 (1, 5) mm Hg/y AVC: 289 (106, 443) AU/y Severe: AVA: 0.0 (−0.1, 0.0) cm²/y V_{peak}: 0.1 (−0.1, 0.2) m/s/y ΔP_{mean}: 3 (0, 5) mm Hg/y AVC: 342 (163, 583) AU/y
Tastet et al (83)	2020	162	3[a]	Echocardiographic evidence of at least mild AS (V_{peak} >2 m/s), without symptoms, enrolled in the PROGRESSA study, and with dual energy x-ray absorptiometry available	Echocardiography	BMD tertile 1: V_{peak}: 2.76 ± 5.4 m/s BMD tertile 2: V_{peak}: 2.73 ± 5.0 m/s BMD tertile 3: V_{peak}: 2.77 ± 5.0 m/s	Overall V_{peak}: 0.11 ± 0.18 m/s/y

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Oxidative stress, related in part to decreased expression and activity of antioxidant enzymes and uncoupling of nitric oxide synthase, has been linked to calcification in aortic valve leaflets (36). Among other sequelae, this converts soluble guanylate cyclase to its oxidized form, thereby reducing its activation, reducing cyclic guanosine monophosphate production, and facilitating procalcific signaling. Ataciguat is nitric oxide–independent soluble guanylate cyclase activator with particular affinity for the oxidized form of soluble guanylate cyclase (37). Preclinical studies demonstrate that ataciguat reduces aortic valve calcification and slows progression of valve dysfunction; early stage clinical studies (CAVS [A Study Evaluating the Effects of Ataciguat (HMR1766) on Aortic Valve Calcification];

TABLE 1 Continued

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Shen et al (84)	2020	141	3.2	Echocardiographic evidence of at least mild AS (V_{peak} >2 m/s), without symptoms, and enrolled in the PROGRESSA study	Echocardiography and CT	Tricuspid: AVA: 1.25 (1.10-1.43) cm² V_{peak}: 2.58 (2.35-2.86) m/s ΔP_{mean}: 14.4 (12.5-18.0) mm Hg AVC: 571 (320-938) AU Bicuspid: AVA: 1.23 (1.04-1.45) cm² V_{peak}: 2.68 (2.49-3.02) m/s ΔP_{mean}: 17.0 (14.7-21.8) mm Hg AVC: 411 (95-1,280) AU	Tricuspid: AVA: −0.05 (−0.095 to 0.0) cm²/y V_{peak}: 0.085 (0.015-0.175) m/s/y ΔP_{mean}: 1.3 (0.2-2.4) mm Hg/y AVC: 93.5 (39.5-163) AU/y Bicuspid: AVA: −0.04 (−0.095 to 0.005) cm²/y V_{peak}: 0.08 (0.00-0.20) m/s ΔP_{mean}: 0.9 (−0.35-2.9) mm Hg/y AVC: 64 (4.5-228.5) AU/y
Pawade et al (49)	2021	150	2	Echocardiographic evidence of AS (V_{peak} >2.5 m/s and grades 2-4 AVC on echocardiography) Prospective, RCT (SALTIRE II)	Echocardiography, CT, and ¹⁸F-NaF positron emission tomography	V_{peak}: 3.36 (2.93, 3.82) m/s ΔP_{mean}: 23 (18, 32) mm Hg AVC: 1,152 (655, 2,065) AU	Placebo: AVA: −0.065 (−0.145, −0.02) cm²/y V_{peak}: 0.165 (0.06, 0.295) m/s/y ΔP_{mean}: 2 (0.05, 4.5) mm Hg/y AVC: 177 (38, 337.5) AU/y Denosumab: AVA: −0.07 (−0.125, −0.04) cm²/y V_{peak}: 0.245 (0.075, 0.375) m/s/y ΔP_{mean}: 3 (0.05, 6) mm Hg/y AVC: 171.5 (99, 402) Alendronic acid: AVA: −0.045 (−0.125, −0.02) cm²/y V_{peak}: 0.22 (0.055, 0.315) m/s/y ΔP_{mean}: 3 (0.05, 4) mm Hg/y AVC: 163 (69, 406.5)

Values are mean ± SD, median (interquartile range), or % (95% CI). Modified with permission from Otto et al (5). ᵃMedian follow-up.

ΔP = transaortic pressure gradient; ¹⁸F-NaF = fluoride F 18 sodium fluoride; apo B = apolipoprotein B; AS = aortic stenosis; ASTRONOMER = Aortic Stenosis Progression Observation: Measuring the Effects of Rosuvastatin; AU = arbitrary unit(s); AVA = aortic valve area; AVC = aortic valve calcification; BMD = bone mineral density; COFRASA = Aortic Stenosis in Elderly: Determinant of Progression; CT = computed tomography; DOAC = direct oral coagulants; GENERAC = Genetic of Aortic Valve Stenosis–Clinical and Therapeutic Implications; Lp-PLA₂ = lipoprotein-associated phospholipase A₂; MDCT = multiple detector computed tomography; PROGRESSA = Metabolic Determinants of the Progression of Aortic Stenosis; RCT = randomized clinical trial; SALTIRE = Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression; SALTIRE II = Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis; SEAS = Simvastatin and Ezetimibe in Aortic Stenosis; V_{peak} = peak aortic valve velocity.

NCT02481258) also suggest that it may slow progression of aortic valve calcification (38).

NOTCH Pathway and noncoding RNAs. Additional promising candidates, not related to lipid metabolism, focus on the NOTCH1 pathway, which is a clear genetic driver of calcific aortic valve disease in humans (39). While NOTCH1 mutations are very rare, multiple modifiers of NOTCH1 protein expression have been identified that lead to hallmarks similar to genetic mutation. Specifically, the long noncoding RNA, H19, and microRNA-34a both suppress NOTCH1 synthesis at pre- and post-transcription stages, respectively (40-43). There are likely multiple other RNAs that alter NOTCH1, which is consequential because loss of NOTCH1 protein expression, via genetic mutation or transcription modification, leads to overexpression of CDH11 by aortic valve interstitial cells (40,42,44). CDH11 enrichment is found in human cases of AS (45), overexpression results in AS in mice (46), and genetic or pharmacologic targeting of CDH11 prevents calcific aortic valve disease and AS in Notch1 mutant mice (47). These findings linking the NOTCH1-CDH11 axis provide hope for possibly identifying a unifying pathobiology of AS by examining modifiers of NOTCH1 expression and also a potential therapy. Unfortunately, further development of the monoclonal antibody to CDH11 (owned by Roche) has been halted after not meeting the primary outcome in a phase 2b clinical trial for rheumatoid arthritis. Thus, new strategies for targeting the NOTCH1-CDH11 pathway, or the RNAs that modify it, are needed.

Mineral metabolism. Calcification is the key process driving the propagation phase of the disease, with calcific deposits increasing mechanical stresses

in the valve and leading to valve injury, inflammation, and further calcification in a vicious cycle that increases valve stiffness and obstruction (48). Successful therapies will need to break this cycle if they are to prove effective. In addition, they will need to exert their anticalcific effects on the valve while maintaining bone health in the elderly population of patients with AS. Given the link between osteoporosis and increased cardiovascular calcification, there was hope that osteoporosis agents might slow AS progression. Indeed, bisphosphonates have anti-inflammatory and lipid-lowering properties. They also prevent myofibroblasts within the aortic valve from differentiating into an osteogenic phenotype, thereby preventing deposition of calcific material in the valve (48). However, the recent SALTIRE II (Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis; NCT02132026) RCT failed to demonstrate an effect of alendronate or denosumab on aortic valve calcification activity using fluoride F 18 positron emission tomography, progression of valve calcium burden using computed tomography-aortic valve calcification (CT-AVC), nor hemodynamic assessments on echocardiography (49). Vitamin K_2 supplementation to potentiate the anticalcific effects of matrix-Gla protein is currently being investigated in the BASIK2 (Bicuspid Aortic Valve Stenosis and the Effect of Vitamin K_2 on Calcium Metabolism on ^{18}F-NaF PET/MRI; NCT02917525) trial, which is also using the same imaging endpoints (50). Other potential anticalcific agents include inositol phosphate analogs that stabilize regions of microcalcification and inhibit vascular calcification in rodents and in vitro models (51).

Hypertension and heart rate. Hypertension increases the diastolic transvalvular pressure gradient and mechanical stress as the valve closes, potentially leading to leaflet injury, inflammation, and endothelial dysfunction. Accordingly, reducing hypertension might slow AS progression in addition to its other cardiovascular benefits (52,53). Related to this, higher resting heart rate may be associated with a faster progression of AS, making it a potential therapeutic target (54).

Future research to identify additional targets and therapies. Beyond use of established preclinical animal models, recent omics efforts that leverage human tissue and exquisite molecular phenotyping are particularly promising for identifying novel therapeutic targets (55). Additionally, meta-analyses or retrospective studies in large databases with reliable medication and serial quantitative echocardiographic data could provide hypothesis-generating insights regarding existing medical therapies associated with slower progression of AS to be tested in prospective RCTs.

IDENTIFICATION OF INDIVIDUALS WITH AS AND RATE OF PROGRESSION

AN UNMET NEED: IDENTIFICATION OF INDIVIDUALS WITH AS. An echocardiogram is indicated for diagnosis of AS, but only in individuals with signs or symptoms suggestive of AS (5), which usually results in diagnosis of AS at a late stage of disease. There is variability in whether cardiac auscultation is performed during a clinical encounter and it is neither sensitive nor specific for diagnosis of AS (56-60). Using auscultation, general practitioners had a sensitivity of 44% and specificity of 69% for detecting significant valvular heart disease; cardiologists were no better with a sensitivity of 31% and specificity of 81% (61). Among individuals ≥65 years of age without a prior diagnosis of valvular heart disease (OxVALVE [Oxford Valvular Heart Disease Population Study] cohort, n = 2,500), systematic echocardiography identified 51% with mild or more left-sided valvular heart disease or moderate or severe right-sided valvular heart disease, including 6.4% with significant (moderate or more) valvular heart disease. For AS specifically, based on the OxVALVE cohort and results from the Cardiovascular Health Study, AS is undetected in 1.3% to 2% of individuals who are asymptomatic and >65 years of age without suspected valvular heart disease, which translates to approximately 1 million adults with undetected AS in the United States (4,62,63). Moreover, ascertainment of symptoms attributable to AS is not straightforward in older adults; early symptoms of heart failure (eg, dyspnea on exertion) may be dismissed as deconditioning or age-related and only further evaluated when they are more overt and severe (eg, orthopnea). The current approach to diagnosis of AS represents an important barrier to identification of patients with early stage AS who would be appropriate candidates for medical therapy trials.

Better tools to detect and diagnose early-stage AS are urgently needed. Although systematic screening with a complete echocardiogram in all individuals over 65 years of age, for example, would likely be cost prohibitive and strain capacity, point-of-care ultrasound could serve as a stethoscope-extender to provide a screening look to detect AS to be followed by a more detailed, complete examination in selected patients (64-67). Routine reporting of valve calcification observed on chest CT scans performed for other purposes may help identify some patients (68). Deep learning-based algorithms for detecting AS using an

TABLE 2	Proposed Eligibility Criteria Considerations for Medical Therapy Trials Targeting the Valve in Individuals With AS
Eligibility Criteria (Ref. #)	**Considerations**
Aortic valve-related	
Morphology (84,98)	Progression rates and drug targets aimed at preventing progression of disease may differ between patients with a bicuspid or trileaflet aortic valve.
Severity of aortic stenosis (3,5,98,100)	Mild to moderate AS is the most appropriate target for medical therapy trials.
	Due to faster disease progression, it will be easier to detect a treatment effect in those with moderate AS, but mild AS may be more responsive to therapy to slow or halt disease progression.
	Aortic valve sclerosis (pre-AS) is difficult to detect, progresses variably and often slowly, and difficult to measure reliably, making it costly and less efficient to study (at least initially).
	Patients at later/severe stages of disease will be less likely to benefit from medical interventions to slow progressive valve obstruction.
Sex (95-97)	Males exhibit more calcification in the leaflets, whereas females tend to have more fibrosis.
Mixed aortic valve disease	Significant concomitant aortic regurgitation may confound symptoms or mask potential benefits of AS therapies.
Severity of symptoms (5)	Patients with severe symptoms are more likely to have hemodynamically significant valve obstruction and are less likely to benefit from medical therapy targeting valve obstruction.
Planned aortic valve intervention	Patients with anticipated aortic valve replacement in the near future should generally be excluded from these trials.
Cardiomyopathy	Temporal variability in myocardial function may confound measurement of the effect of therapy on hemodynamic progression (eg, V_{peak} may be influenced by variability in stroke volume rather than changes in valve obstruction).
	Symptoms in patients with impaired myocardial function may be difficult to attribute to the valve vs underlying cardiomyopathy.
Concomitant cardiovascular comorbidities	
Other valvular heart disease (5)	Assessing symptoms caused by AS is challenging in the setting of other significant valvular lesions.
	Patients may be less likely to benefit from medical therapy interventions for AS when other valve disease is present.
Coronary artery disease (5)	Assessing symptoms caused by AS may be challenging in the setting of significant coronary artery disease.
	Because of overlap in the pathobiology of AS and atherosclerotic disease, patients with coronary artery disease may already be on medications affecting a pathway being targeted by an investigational therapy for AS.
Cerebrovascular disease	Prior cerebrovascular disease may account for thrombotic complications in patients with AS.
Atrial arrhythmias (atrial fibrillation/atrial flutter)	Thromboembolic events in patients with atrial arrhythmias might not be caused by the study treatment.
Age (95)	Depending on the therapeutic target, investigators may need to consider enrolling younger vs older patient populations.
	Age cutoffs for studies should be determined based on mechanism of action and anticipated time period needed to observe benefit of the medical intervention for AS.
Frailty, limited life expectancy, or severe multimorbidity or end-stage organ dysfunction (5)	Patients with significant frailty, limited life expectancy, or severe multimorbidity or end-stage organ dysfunction may be less likely to survive study duration or experience benefits attributed to medical therapies for AS.
	Significant end-organ dysfunction (eg, chronic kidney disease) may influence pathophysiology and the degree to which a prospective therapy may effectively slow AS progression.

electrocardiogram show promise in preliminary studies (69). Investment in studies to identify and to validate reliable, scalable, and cost-effective tools to screen for and detect AS at an early stage of disease in diverse populations is critical to and would be synergistic with efforts to identify and test novel therapies and treatment strategies and eventually apply effective therapies to those who would benefit.

RATE OF PROGRESSION OF AS. Determining the sample size needed to ensure statistical power and defining the appropriate enrollment criteria for clinical trials testing medical therapy aimed at slowing disease progression depend on reliable data on average disease progression rates, variability in those

estimates, and factors that affect the rate of disease progression in individual patients. Several prospectively and retrospectively conducted studies have informed current understanding of the rate of AS progression (22,70-94) (**Table 1,** Supplemental Table 1). These studies typically have enrolled patients who are asymptomatic with mild to moderate AS and described the rates of progression of AS in allcomers, specific clinical subgroups, or in the setting of medical therapy interventions, such as cholesterollowering therapy with β-hydroxy β-methylglutarylcoenzyme A reductase inhibitors (ie statins) or agents targeting vascular calcification (12,21,22,49,74). Severity and progression of AS have been defined by several key parameters, including aortic valve area

(AVA), peak transvalvular velocity (V_{peak}), and mean transvalvular pressure gradient by Doppler echocardiography. These studies show heterogeneous rates of AS progression and associated variance with an annualized increase in V_{peak} ranging from 0.08 and 0.0.40 m/s/y and reduction in AVA between −0.03 and −0.16 cm²/y. Annualized rates of change in AVC score derived by CT also vary between patient populations ([74],[77-82],[84],[94]).

The available data suggest variability in terms of AS progression, with rates depending on severity at initial assessment and presence of other risk factors that contribute to rapid progression of disease. Limitations common to many prior studies include variable reporting of baseline and follow-up AS assessment by echocardiographic and CT measures, lack of standardized follow-up imaging and clinical protocols between studies, small sample sizes, and limited long-term follow-up duration extending beyond 5 years after baseline measurements. Consequently, robust estimates regarding average rates of progression (and associated variances of these rates) are lacking, and as such, power estimates for designing medical therapy trials with imaging end points are inherently limited. Future investigations will need to focus on standardizing eligibility criteria and imaging assessments (both echocardiography and CT) to allow for comparison of findings between studies to better inform estimates regarding progression of disease severity. Furthermore, larger studies and longer-term follow-up are required for annualized estimates of rates of progression of AS beyond the first few years of enrollment. Improvements in study design will help better define the natural history of AS and identify the patient populations at highest risk for rapid progression of disease.

AS MEDICAL THERAPY TRIAL ENROLLMENT POPULATION AND ELICITING THE PATIENT VOICE

TRIAL ENROLLMENT POPULATION. The primary goal of medical therapy targeting the progression of valve obstruction is to delay or, ideally, obviate the need for AVR. However, despite completion of several RCTs evaluating the effects of medical therapy interventions for patients with AS ([12],[21],[22],[49],[74]), no effective therapies have been identified. To optimize the efficiency and increase the likelihood of successful matching of therapy with the appropriate target population, several eligibility criteria need to be considered and tailored to the specific intervention being evaluated, including severity of AS, age, sex, valve morphology, symptom status, comorbidities, and life expectancy (**Table 2**). Comorbid conditions such as cardiomyopathy, other forms of valve disease, coronary artery disease, arrhythmias, and other cardiovascular diseases may present challenges in assessing the efficacy of the medical therapies to treat AS because attributing study end points to AS vs comorbid conditions may not be possible.

AVR is the standard of care for patients who are symptomatic with severe AS; thus, medical therapy trials will focus on patients who are not yet experiencing symptoms related to their AS. Until effective therapies are identified, enrolling individuals with aortic sclerosis is unlikely to provide useful results because progression from sclerosis to stenosis occurs in only a subset of patients over many years, thus requiring larger trial sample sizes and a longer study duration. On the opposite end of the spectrum, once AS has become more end-stage (severe or near severe), medical therapy to slow progression of valve obstruction is unlikely to be beneficial unless such a therapy is anticipated to rapidly reverse or halt calcification and hemodynamic progression.

Even within mild to moderate stages of AS, pathobiology is influenced by relative severity of AS, sex, age, and valve morphology, each of which may influence the likelihood of a given therapy slowing disease progression. Less severe AS is characterized more by inflammation, whereas later stage disease is more fibrocalcific. Several studies have consistently demonstrated an association between sex and calcium burden in aortic valve leaflets. Women have lower amounts and density of calcification and more fibrosis in their leaflets than men do for a given severity of AS ([95-97]). Older age, too, has been linked to greater leaflet calcification ([95]). Interestingly, the number of cardiac risk factors was associated with faster AS progression in patients with a bicuspid but not trileaflet valve ([98]). After adjustment for age and sex, a bicuspid valve may be associated with faster disease progression, but results are mixed ([84],[98]).

Beyond accounting for the influence of the above-mentioned factors on likelihood of responsiveness to a specific therapy, enriching study populations for patients who are at risk for rapid progression of disease will improve efficiency and reduce the costs of these studies. The strongest predictors of disease progression are baseline assessments of valve calcification and hemodynamic severity ([98-100]). Patients with moderate AS progress faster than patients with milder disease do, thereby making it easier to demonstrate a treatment effect in those with moderate disease. Whereas historic examples of medical therapy trials have used echocardiographic or CT-

based imaging findings to help select potential candidates for enrollment and then to follow changes in these parameters in response to study interventions, novel molecular imaging modalities may provide additive insights regarding aortic valve pathobiology and predisposition for faster progression, including information on processes that drive inflammation, remodeling, and calcification, all of which are critical components of AS (101). To date, ^{18}F-sodium fluoride (^{18}F-NaF) and ^{18}F fluorodeoxyglucose have been evaluated for their potential roles in evaluating calcification and inflammation in the setting of AS (102,103); ^{18}F-NaF has demonstrated the most potential to identify active disease and patients at risk for progression.

Other clinical factors and biomarkers associated with faster progression could serve as enrichment criteria for trials, including metabolic syndrome (104), diabetes mellitus (91), vitamin K antagonists (81), lipoprotein-associated phospholipase A_2 levels (76), apo B-apo A-I ratio (79), Lp(a) (105), and oxidized phospholipids on apo B-100 (105). A growing body of evidence suggests that a number of genetically-influenced factors may contribute to development and progression of AS (23,106,107). Last, machine learning algorithms have demonstrated great potential to use large-scale data sets to augment available risk-stratification and prediction models, as reported in a recent analysis that suggested the possibility for identifying distinct phenotypes of AS severity (108,109). Such strategies may allow for selection or enrichment of patients at highest risk for rapid disease progression.

ELICITING THE PATIENT VOICE. Even though shared decision making, including the process of identifying individual patient goals for therapy as defined by patients themselves, is recommended in current guidelines (5), this process is often quite perfunctory and is not widely implemented in a comprehensive manner with the use of specific skill sets and decision aids. Specifically, in patients with AS, little is known about which treatment goals are most important, how patients compare their options, and how their own preferences are integrated into decision making (110). It will be essential to include patients in the *design* of clinical trials of early medical interventions aimed to prevent progression of AS. Several patient advocacy organizations (eg, Heart Valve Voice US, Mended Hearts) have developed programs to train patients with heart valve disease to participate in the design and conduct of research. Benefits of patient engagement include early understanding of which patient populations to target (ie, stage of disease

TABLE 3 Considerations for Patient Goals and Preferences for Medical Therapy Trials in AS
Patient population
Age
Comorbidities
Historically underrepresented patients receiving therapy or participating in trials (eg, women, minorities, rural patients)
Type of valve disease (bicuspid vs trileaflet aortic valve)
Stage of disease (sclerosis vs mild vs moderate AS)
Native valve disease only vs post-AVR
Trade-offs
Medication for an asymptomatic condition vs avoiding or delaying AVR
Varying types of side effects of medication: physical symptoms, inconvenience, economic
Uncertainty regarding whether AVR will eventually be indicated during remaining life years
Implementation barriers to trial enrollment and strategies to address
Patient perception of randomization vs observational study design
Reaching underserved populations
Trust in medical system
Education on disease process
Consistent methodology for measuring and incorporating patient preferences
Drug delivery (daily vs multiple doses, oral vs subcutaneous vs intravenous)

AS = aortic stenosis; AVR = aortic valve replacement.

progression), patient views on medical interventions, clarity on potential implementation hurdles for trial enrollment, and impact on diverse populations. Furthermore, when designing clinical trials, patient input early in the process can assist in selecting trial outcomes that are meaningful to the patients for whom the intervention is intended, identifying trial operations acceptable to patients (ie, number and type of study visits), and promoting recruitment and retention of diverse patients through patient-oriented materials (111,112). Interventions such as these are shown to improve patient engagement in trials (112), improve adherence to study protocols, and are often cost-effective (111).

The U.S. Food and Drug Administration (FDA) has focused for several years on refining recommendations for the incorporation of the patient voice in both study design and drug and device approval. In 2016, the FDA published a patient preference information (PPI) white paper (113), targeted at investigators and industry-leading clinical trials. The FDA encourages submission of PPI and provides guidance on the conduct of PPI studies. PPI is most relevant in decisions that are "preference sensitive" as in the case of AS. Preference sensitive decisions are when: 1) there is more than 1 valid treatment option; 2) data supporting one option over another is limited; and 3) patient goals and preferences vary in how they weigh risks and benefits of the choices.

TABLE 4   Imaging Endpoints and Tools for Assessing Aortic Stenosis Progression

Imaging Modality	Measure(s) of AS Severity	Advantages	Limitations
Valve			
Echocardiography	*Hemodynamic assessment* • Peak velocity • Mean gradient • Aortic valve area	Most widely used in clinical practice No radiation exposure Relatively inexpensive Main imaging method used to guide AVR	Poor progression to noise ratio Relatively large patient sample sizes required to demonstrate a treatment effect Most measures dependent upon LV flow (LV flow may change on follow-up)
CT aortic valve calcium scoring (CT-AVC)	*Structural assessment* • Quantification of the aortic valve calcium burden	Favorable progression to noise ratio Relatively small patient samples sizes to demonstrate an effect Flow independent measurements Widely available at most centers Low per scan costs	Radiation exposure Ignores the contribution of fibrosis to aortic stenosis severity and progression
Contrast CT angiography	*Structural assessment* • Quantification of the aortic valve fibro-calcific burden	Equipment is widely available at most centers Assesses the burden of both valve calcification and fibrosis Flow independent measurement Widely available at most centers	Novel technique that is currently not well validated. Time consuming image analysis methodology Progression to noise ratio not yet established Requires contrast administration
PET/CT	*Disease activity assessment* • 18F-NaF uptake as marker of calcification activity	Assessment of calcification activity – a pathophysiologic mechanism that could be targeted by therapeutics Highly reproducible As an assessment of disease activity may change more quickly than structural or hemodynamic assessments	Expensive Radiation exposure Only available at specialized centers Ignores the contribution of fibrosis to aortic stenosis severity and progression
Myocardium			
Echocardiography	• LV mass • Global longitudinal strain • Ejection fraction	Widely used in clinical practice No radiation exposure Low per scan costs Main imaging method used to guide AVR	Poor precision in measurement Progression to noise not known Relatively high number of patients required to demonstrate a treatment effect
CMR	• LV Mass • Myocardial fibrosis • Ejection fraction	No radiation exposure Improved precision in measurements compared to echocardiography Relatively small number of patients required to demonstrate a treatment effect	Higher per scan costs than echo but lower sample sizes required Requires contrast administration

AVC = aortic valve calcium; CMR = cardiac magnetic resonance; CT = computed tomography; LV = left ventricular; PET = positron emission tomography; other abbreviations as in **Table 3**.
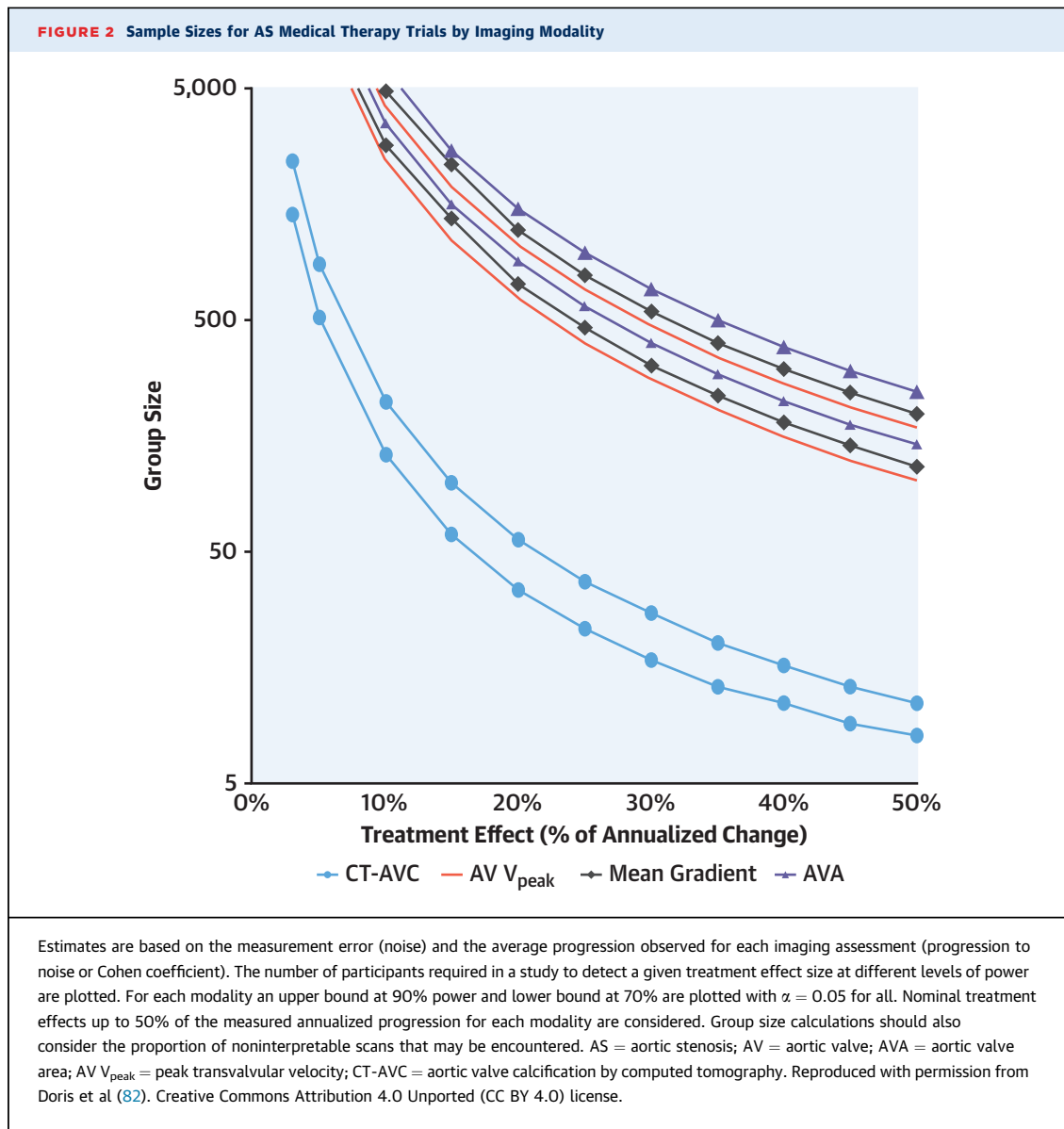
Specifically, PPI can assist investigators and other stakeholders in understanding how patients' conceptualize the choice of a medical or device therapy, how they prioritize or weigh risks and benefits, and the extent to which these preferences may vary across diverse populations, particularly those traditionally under-represented in cardiovascular clinical trials (eg, women, African American, Latinx populations).

One of the central issues in which PPI may be informative when considering medical therapy is the willingness of the affected patient population to consider taking a medication for prevention of disease progression. Notably, barriers exist for well-established medications: 50% of patients are nonadherent to their medications in primary prevention for cardiovascular disease (114). In primary prevention for heart disease and stroke, researchers identified the burden of taking multiple medications and focused intervention studies on the role of a polypill (115). Yet, when examining the effectiveness of such as intervention, researchers required 80%

adherence prior to being randomized in the study; 1 in 4 patients initially screened did not go on to the randomized study.

Interventions that require patient action are inherently complex and related to patients' unique context. Indeed, medication adherence trends are affected by race and sex (116,117). In the area of stroke prevention in the setting of atrial fibrillation, disparities in adherence to medications are seen in some studies by sex but not in differing levels of health literacy (118). Poor adherence may be mitigated when the medication regimen is simplified, as in once-a-day dosing and no requirement for monitoring (119).

It is thus imperative to plan for PPI studies in trial design for studies testing therapies for AS, because patients will be weighing a trade-off of 1) adhering to a medication for years to avoid (or delay the need for) an AVR vs 2) avoiding an additional medication and face the decision of AVR as "bail out" therapy if their AS becomes severe. There remains uncertainty as to how many patients with mild AS will go on to need AVR with close follow-up (120). and it will be

FIGURE 2 Sample Sizes for AS Medical Therapy Trials by Imaging Modality

Estimates are based on the measurement error (noise) and the average progression observed for each imaging assessment (progression to noise or Cohen coefficient). The number of participants required in a study to detect a given treatment effect size at different levels of power are plotted. For each modality an upper bound at 90% power and lower bound at 70% are plotted with α = 0.05 for all. Nominal treatment effects up to 50% of the measured annualized progression for each modality are considered. Group size calculations should also consider the proportion of noninterpretable scans that may be encountered. AS = aortic stenosis; AV = aortic valve; AVA = aortic valve area; AV V$_{peak}$ = peak transvalvular velocity; CT-AVC = aortic valve calcification by computed tomography. Reproduced with permission from Doris et al (82). Creative Commons Attribution 4.0 Unported (CC BY 4.0) license.

important to understand how patients view this uncertainty. Several additional considerations to PPI studies in this context will need to be considered (**Table 3**).

TRIAL ENDPOINTS AND ASSESSMENT

RATIONALE FOR IMAGING ENDPOINTS ASSESSING DISEASE PROGRESSION.
AS is a slowly developing condition that is often monitored in the clinic for many years if not decades. Traditional clinical end points, such as time to AVR or death, accrue over similarly long periods. RCTs based on clinical end points are therefore challenging, requiring very large patient populations and long durations of follow-up.

This makes them expensive and unattractive to pharmaceutical companies and research funders. An alternative strategy is therefore required, at least initially.

Progressive valve narrowing is the hallmark of AS. Without it, patients do not develop left ventricular decompensation, symptoms, or clinical events, nor are they considered for AVR. Given this tight linkage, any therapy that can effectively slow disease progression should also delay or obviate AS-related clinical events; in this sense, "disease progression" (ie, progressive valve narrowing) is ostensibly a face-value surrogate for clinical events/outcomes. Accordingly, to the degree that an imaging modality can accurately measure disease progression, it seems

TABLE 5   Potential Clinical (Event) Endpoints, Including Advantages And Limitations

Clinical Endpoints	Details	Advantages	Limitations
AS-related endpoints			
Aortic valve replacement	TAVR or SAVR with or without coronary bypass grafting / aortic root replacement	• Clinical endpoint attributable to the disease process being modified • Easy and accurate to capture – may be available from electronic patient records and data linkage • The major intervention that patients and physicians are keen to avoid	• Requires large trials and/or prolonged follow-up (~5-10 y) • Optimal timing of AVR not yet established (strategies may differ between institutions and likely to change within the follow-up period of future trials)
Unplanned aortic stenosis related hospital admission	An unplanned hospital admission with syncope, heart failure, chest pain, or arrhythmia (ventricular arrhythmia or second- or third-degree heart block) attributed to AS	• Clinical endpoint attributable to the disease process being modified	• Requires large trials and/or prolonged follow-up (~5-10 y) • Patients with AS often have comorbid conditions that may account for the clinical events, rather than being caused by AS
AS-related death	Death related to aortic stenosis (sudden cardiac death, death caused by heart failure, ventricular arrhythmia or AV conduction disease in a patient with severe aortic stenosis)	• Clinical endpoint attributable to the disease process being modified	• Requires large trials and/or prolonged follow-up (~5-10 y) • Adjudication may be challenging in the context of co-morbidities such as coronary artery disease
Symptoms, disability and quality of life			
Symptoms	Shortness of breath Chest pain Presyncope and syncope	Important to patients	• Requires large trials and/or prolonged follow-up (~5-10 y) • May be attributable to co-morbidities rather than AS
Quality of life assessments	Kansas City Questionnaire 6-minute walk test	Important to patients	• Requires large trials and/or prolonged follow-up (~5-10 y) • Changes may be attributable to co-morbidities or frailty rather than AS
Disability-Free years	Number of years a patient lives free from disability	Important to patients	• Requires large trials and/or prolonged follow-up (~5-10 y) • Changes may be attributable to co-morbidities or frailty rather than AS
Safety endpoints			
Atherothrombotic events	Myocardial infarction Stroke	Important safety data for drugs without a safety profile	• Requires large trials and/or prolonged follow-up (~5-10 y) • Events are related to atherosclerosis not AS
Coronary revascularization	Coronary artery bypass grafting Percutaneous coronary intervention	• Important safety data for drugs without a safety profile • Decisions to proceed with revascularization may be triggered by progression in AS	• Requires large trials and/or prolonged follow-up (~5-10 y) • Events are related to atherosclerosis not AS
Death	All-cause mortality	• Important safety data for drugs without a safety profile • Potentially available from electronic patient records and data linkage • No need for adjudication	• Requires large trials and/or prolonged follow-up (~5-10 y) • Events may not be related to AS but rather co-morbidity

SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; other abbreviations as in **Table 3**.

warranted to perform RCTs testing medical therapy for AS with imaging endpoints evaluating progression of valve disease as the primary efficacy end point. Because imaging endpoints are measured on a continuous scale and can be assessed longitudinally (allowing for repeated measures analyses), statistical power for detecting an effect is substantially increased (with resulting decreases in sample size) compared with dichotomous endpoints (121). Accordingly, imaging endpoints would facilitate more

rapid, efficient, and cost-effective identification of the most promising therapeutic candidates and discarding of the ineffective.

POTENTIAL IMAGING ENDPOINTS. Determining the optimal imaging end point to track disease progression and response to therapy depends on numerous factors including expense, precision, radiation exposure, and availability. Importantly, when powering an RCT, 2 key imaging factors determine the required

sample size and duration of follow-up: 1) the measurement error (noise) of the specific technique; and 2) its average progression over time. This leads to the concept of the progression-to-noise ratio (also known as the Cohen statistic) (82).

International clinical guidelines recommend assessing AS severity with echocardiography as well as CT-AVC scoring when echo assessments are discordant (5,122). Currently these 2 imaging modalities are also the most attractive imaging endpoints for RCTs. In addition, novel assessments including contrast CT angiography (123) and molecular assessments of disease activity, such as ^{18}F-NaF positron emission tomography (103), are promising, each with their own potential advantages and disadvantages (Table 4).

Echocardiography is the first-line clinical imaging test for AS with decisions to proceed to AVR made on the basis of AVA and transvalvular gradients (5). For these reasons, echocardiography is a key end point in potential future trials. However, hemodynamic echocardiographic assessments are sensitive to small changes in flow status and misalignment of the Doppler beam with the aortic valve jet. Consequently, they are hampered by relatively poor measurement precision and progression-to-noise ratio (82).

CT-AVC has emerged as an alternative assessment of AS severity, providing a structural, flow-independent assessment of the calcium burden in the valve. Using sex-specific thresholds, CT-AVC demonstrates good accuracy vs echocardiography and provides powerful prognostic information (99,100,124). In the context of clinical trials, the progression-to-noise ratio is 4-fold better than for echocardiography, indicating a superior ability to detect changes in disease severity over time. Indeed, recent data suggest that >10-fold fewer patients would be required to detect 10%, 20%, and 30% treatment effects using CT-AVC (165, 43, and 20 patients, respectively) compared with the best performing echocardiographic assessment (V$_{peak}$: 3,142, 787, and 351 patients, respectively) (Figure 2) (82). This makes a strong argument for using CT-AVC alongside echocardiography in phase 2 trials, although the proportion of noninterpretable CT scans (∼10%-15%) must also be considered in sample size calculations, and it should be remembered that CT-AVC does not account for the effects of therapy on valve fibrosis.
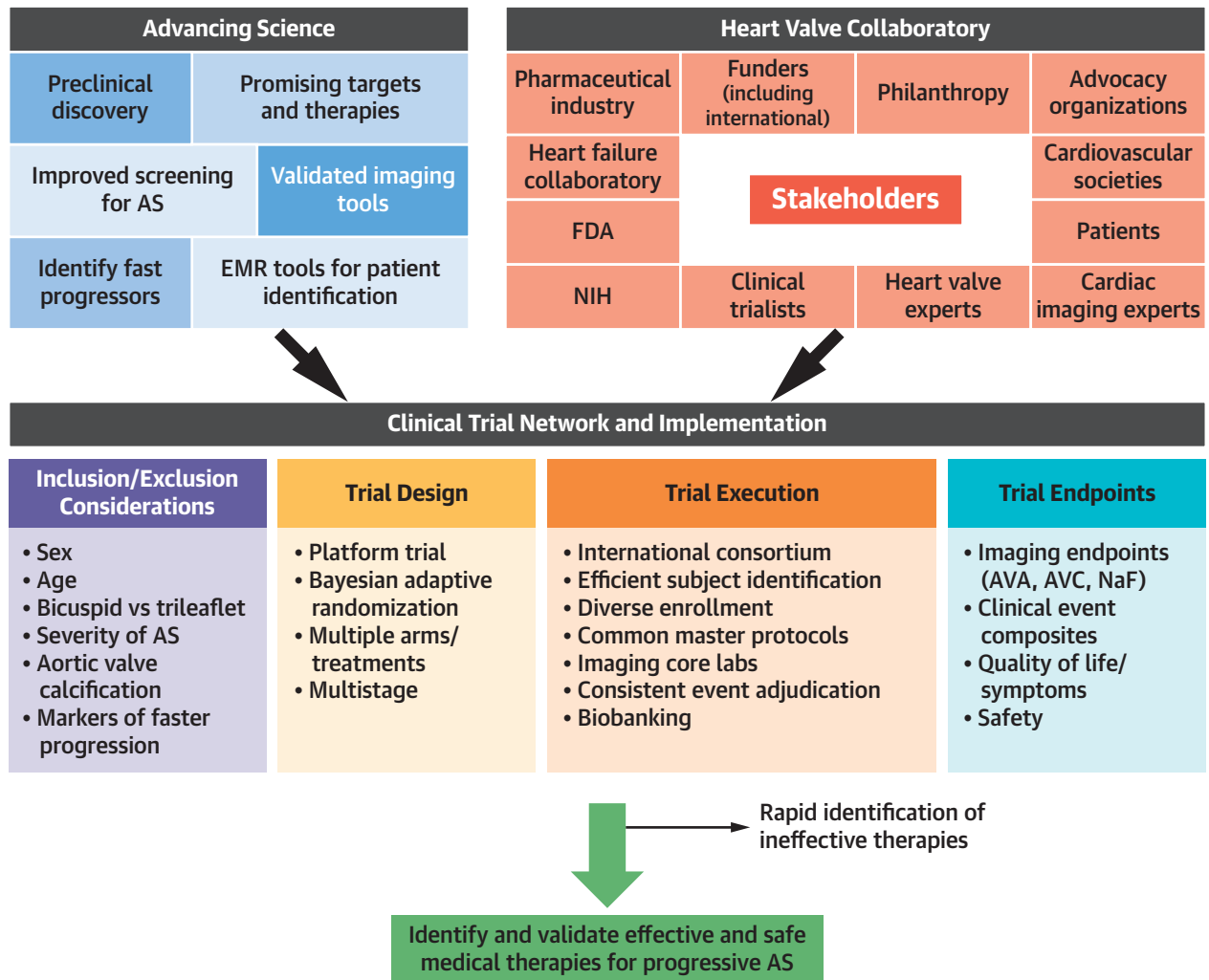
CLINICAL EVENT END POINTS FOR AS TRIALS. All clinical outcomes or events assessed should be patient-centered insofar as they are meaningful to patients—how they feel, function, or survive—either directly or indirectly. Several such outcomes could be considered for assessment of medical therapies targeting AS, each with potential advantages and disadvantages (Table 5). Beyond patient-centeredness, broadly there are 2 potential motivations for including a particular clinical feature in a medical therapy trial for AS: 1) the endpoint is thought to be affected by and related to progression of valve disease (eg, hospitalization for heart failure, aortic valve intervention); or 2) it is a safety endpoint that is important to include even if not directly related to progressive valve obstruction (eg, osteoporosis, type 1 myocardial infarction, stroke).

The development of composite clinical endpoints that combine sequelae of AS is desirable. Greater power is achieved with more severity levels of the outcome assessment, more times at which it is assessed, and longer follow-up duration. These composite endpoints would include components such as AVR, AS-related hospital admission, and AS-related death. Definitions for the latter 2 are not well established but can be addressed (Table 5) and outlined in a future consensus document. Non-AS-related clinical events (eg, non-CV death, type 1 myocardial infarction, stroke) could be collected separately to assess the safety of any potential drug, particularly in those without an existing clinical and safety track record. Symptoms and quality of life assessments are important to patients, although symptoms will often reflect comorbidities rather than AS. Selection of appropriate clinical end points will be influenced by the stage of AS enrolled in the trial. For example, if patients with aortic valve sclerosis and mild AS are enrolled, quality of life related to valve function is unlikely to deteriorate and clinical endpoints such as death or AVR are unlikely to accrue at a meaningful rate over 2 to 3 years. In contrast, if patients with moderate AS are enrolled, then imaging endpoints along with patient-centered clinical outcomes should be included because the development of symptomatic severe AS will occur sooner.

RECOMMENDED STRATEGY. Ultimately imaging endpoints need to be agreed on by multiple stakeholders, including the FDA. Given the complementary strengths of echocardiography and CT-AVC, 1 potentially attractive strategy would be to measure disease progression with both CT-AVC and echocardiography. If an intervention demonstrates efficacy on CT calcium scoring, then further recruitment and follow-up can ensue until there is sufficient power to detect an effect on echocardiographic endpoints. Addition of CT angiography to the CT protocol would be ideal to not only provide additional data on disease progression alongside other modalities but to also anticipate the possibility that future studies may demonstrate

CENTRAL ILLUSTRATION Overarching Approach to Evaluate Medical Therapy for Calcific Aortic Stenosis

Advancing Science

Preclinical discovery	Promising targets and therapies
Improved screening for AS	Validated imaging tools
Identify fast progressors	EMR tools for patient identification

Heart Valve Collaboratory

Pharmaceutical industry	Funders (including international)	Philanthropy	Advocacy organizations
Heart failure collaboratory	**Stakeholders**		Cardiovascular societies
FDA			Patients
NIH	Clinical trialists	Heart valve experts	Cardiac imaging experts

Clinical Trial Network and Implementation

Inclusion/Exclusion Considerations	Trial Design	Trial Execution	Trial Endpoints
• Sex • Age • Bicuspid vs trileaflet • Severity of AS • Aortic valve calcification • Markers of faster progression	• Platform trial • Bayesian adaptive randomization • Multiple arms/ treatments • Multistage	• International consortium • Efficient subject identification • Diverse enrollment • Common master protocols • Imaging core labs • Consistent event adjudication • Biobanking	• Imaging endpoints (AVA, AVC, NaF) • Clinical event composites • Quality of life/ symptoms • Safety

Rapid identification of ineffective therapies

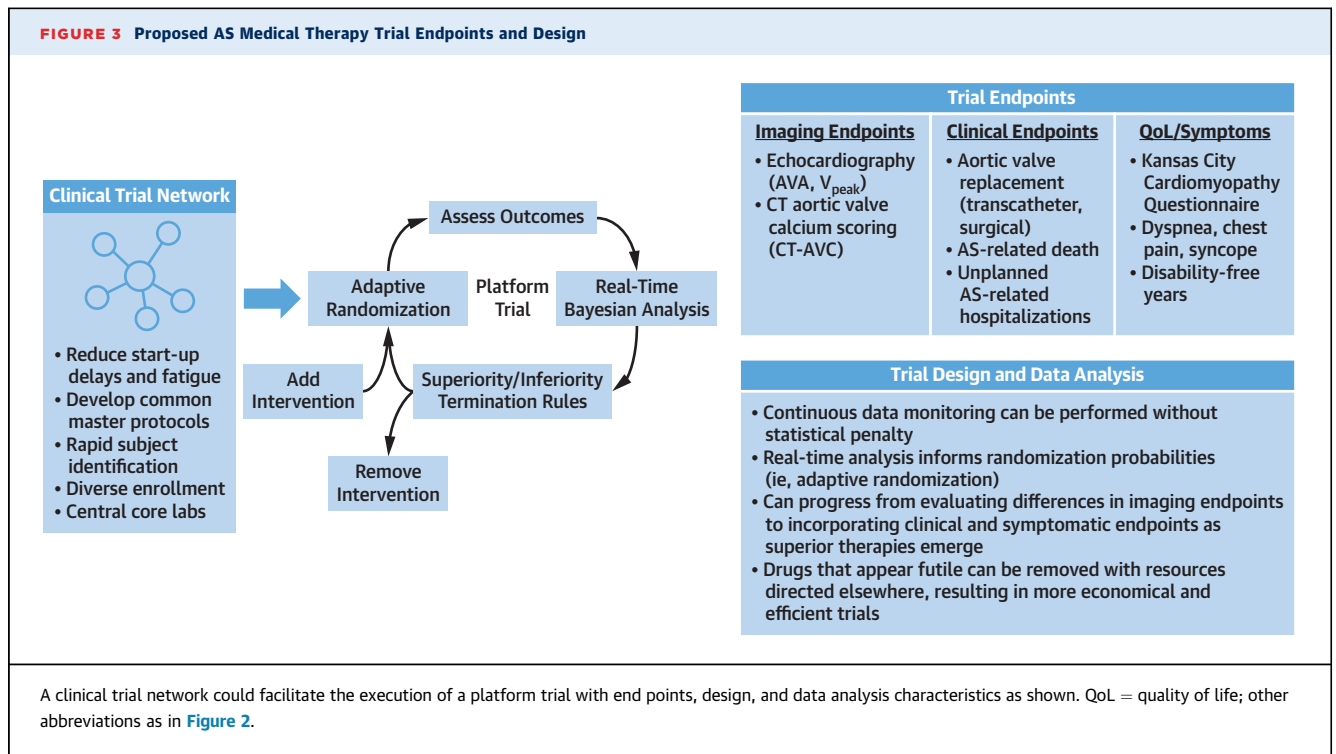Identify and validate effective and safe medical therapies for progressive AS

Lindman, B.R. et al. J Am Coll Cardiol. 2021;78(23):2354–2376.

Scientific advances in key areas combined with collaboration across multiple stakeholders (facilitated by the Heart Valve Collaboratory) could establish a clinical trial network purpose-fit to implement a platform trial to identify and validate effective and safe medical therapies for progressive aortic stenosis. AVA = aortic valve area; AVC = aortic valve calcification; EMR = electronic medical record; FDA = U.S. Food and Drug Administration; NaF = sodium fluoride; NIH = National Institutes of Health.

contrast CT to be the optimal way to track progression of valve pathology, given its ability to assess both calcific and fibrotic valve thickening in an integrated manner.

Given the current lack of any effective medical treatments for AS (large unmet need) and the mechanism by which AS causes clinical events—fundamentally and necessarily through progressive valve narrowing—we propose that a drug that slows AS progression based on imaging end points would

warrant full FDA approval or at least accelerated approval (125). If full approval based on an imaging end point was acceptable, perhaps directional (but not statistically significant) benefits on clinical outcomes would be sufficient to reinforce the efficacy and benefit of the drug in the absence of any concerning safety data. Accelerated approval, however, is "subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit" (125). Presumably this would entail

FIGURE 3 Proposed AS Medical Therapy Trial Endpoints and Design

A clinical trial network could facilitate the execution of a platform trial with end points, design, and data analysis characteristics as shown. QoL = quality of life; other abbreviations as in **Figure 2**.

demonstrating that the drug also reduces AS-related clinical events (eg, death, valve intervention, AS-related hospitalization, quality of life). Because such evidence would need to come from a placebo-controlled randomized trial and owing to the difficulty of enrolling in such a trial once accelerated approval is given, such a clinical outcome trial would likely need to be in the later stages of follow-up before accelerated approval was granted. Rather than running 2 separate and sequential trials, the first with an imaging endpoint and the second with a clinical endpoint, the most efficient way to meet the requirement to "verify and describe" the clinical benefit would be to run a single trial with 1 study population with an earlier (~1-2 year) imaging-based endpoint examining progression and a later endpoint examining clinical outcomes. If there was no beneficial effect of the drug on the imaging endpoint, the trial could be stopped; if the drug slowed AS progression by an imaging end point, then accelerated approval could be granted when the trial had reached adequate enrollment and follow-up to ensure that a determination on clinical benefit could be made. Such a trial would also enable investigators to test whether AS progression rate (assessed by imaging) is associated with subsequent clinical outcomes and test whether a drug's reduction of AS progression rate mediates the benefit of the drug on

clinical outcomes. This would reinforce the validity of AS progression as a clinically meaningful surrogate end point, thereby potentially allowing full approval (rather than accelerated approval) to be granted to drugs that demonstrate a beneficial effect on AS progression assessed by imaging in future trials. The safety data required by the FDA will likely depend on whether the drug is novel or has some prior track record.

IMPLEMENTATION AND DESIGN OF CLINICAL TRIALS. There are many barriers to the development of an effective medical therapy for AS including a lack of funding partnerships, an international consortium of sites to conduct trials in this population efficiently, and interest from the pharmaceutical industry (11). Many of these challenges may be overcome by engaging key stakeholders to create a clinical trials network with the goal of efficiently designing and testing promising medical therapies to slow the progression of AS (**Central Illustration**). The power of clinical trial networks have been demonstrated in multiple domains including heart failure (126), acute lung injury (127), and cardiothoracic surgery (128) to name a few. For instance, since 2008 the National Heart, Lung, and Blood Institute-funded Heart Failure Clinical Research Network has completed 13 multicenter clinical trials that have rapidly informed contemporary heart failure

management and provided strong evidence for the benefits of such clinical trial networks (126).

Given the prevalence of AS and the lack of proven medical therapies, there is enormous potential for the development of a clinical trial network in this domain. Such a network could reduce start-up delays and fatigue associated with launching clinical trials and would oversee the development and administration of common master protocols so that new candidate therapies in the pipeline may be tested in a rapid and efficient manner (**Figure 3**). Moreover, the clinical trial network could support and oversee central core labs for consistent and reliable evaluation of imaging end points (eg, CT, echocardiography), clinical event adjudication, and biobanking. Finally, the selection of participating clinical sites would be dependent on several factors including the sites' ability to identify and to recruit patients rapidly throughout the continuum of AS severity, the availability of multimodality imaging expertise in AS including echocardiography, CT, and positron emission tomography/CT, and the presence of diverse clinical champions to oversee the success of trials at each site. Sites would also be selected to help ensure enrollment of a diverse study population that includes patients traditionally under-represented in clinical trials such as women and minorities (129,130).

Concurrent with the identification of potential participating international clinical sites, engaging diverse funding agencies including international governmental agencies (eg, National Institutes of Health, Centers for Medicare and Medicaid Services, Canadian Institutes of Health Research), cardiovascular societies, and philanthropic organizations will be critical to establishing a clinical trial network. Next, in collaboration with patient advocacy groups, pharmaceutical industry partners, and governmental regulatory agencies (ie, FDA), clinical trials of promising medical therapies can be designed with the goal of efficiently identifying safe and effective therapies while providing sufficient evidence for their approval by international regulatory agencies.

Given the number of potential medical therapies for the treatment of AS (see the discussion of promising targets), a clinical trial network could consider novel trial designs such as adaptive multiarm, multistage trial designs—platform trials—to efficiently allow for multiple medical therapies to be compared with a common control group as was demonstrated in the RECOVERY (Randomised Evaluation of COVIS-19 Therapy; NCT04381936) trial testing therapies for severe acute respiratory syndrome coronavirus 2 (131,132) (**Figure 3**). Recently, Pawade et al (49) moved in this direction when they conducted a randomized

controlled trial testing the efficacy of 2 individual drugs, denosumab and alendronic acid, to prevent the progression of AS by separately comparing these 2 agents against a common control group.

A platform trial could take advantage of biostatistical techniques such as Bayesian adaptive randomization where the probability of randomization may be altered based on continuous data monitoring to adjust the sample size needed to ensure futile studies end sooner and promising interventions reach a definitive conclusion (**Figure 3**) (133,134). As compared with frequentist trial designs, real-time continuous data monitoring can be performed without statistical penalty in Bayesian designs as frequent analysis of the data does not alter the method by which the probability of treatment effect is computed (121,135). Given that the vast majority of treatments that enter development are unsuccessful, adaptive platform trials represent a statistically efficient method of identifying successful therapies. If a drug appears to be futile, instead of continuing that arm of the trial, it can be removed and resources can be directed elsewhere. Indeed, the FDA has endorsed the design and implementation of adaptive clinical trials (136).

However, in contrast to some seminal platform trials such as I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis 2) (137) and REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) (138), where endpoints are assessed over the course of months, among the challenges of adaptive trial designs for AS is that detectable progression of disease can be slow, often occurring over years. This long time course may make it impractical to implement meaningful trial adaptations over short time periods. Nevertheless, depending on the chosen study population (those with early vs late disease), primary endpoints selected, and the planned duration of the trial, a Bayesian adaptive clinical trial may be feasible and could result in a more efficient trial. Some of these challenges may be partially attenuated if the trial could be enriched with a population of patients that are most likely to progress quickly.

Building the infrastructure to operationalize a platform trial would require a commitment to and focus on the disease with the goal of finding effective treatment(s) as a higher priority than the evaluation of any particular experimental therapy (131). Coordination and financial support of multiple stakeholders would be essential. Given the societal costs of AS, there is strong rationale for government funding.

Pharmaceutical companies may trade loss of control over the study design and execution for the substantially lower cost of testing the efficacy of their specific drug. The advantages of a platform trial would extend to patients who have access to a greater number of experimental therapies and benefit from response-adaptive randomization and to investigators who can evaluate for potential synergy between treatments and leverage a larger and more heterogeneous study population to quantify differences in treatment effects in subgroups.

CONCLUSIONS

The aging of the population and the large and increasing number of individuals with AS combined with the current lack of any effective medical therapy to slow disease progression and the dearth of RCTs testing promising therapies provide a clarion call for action. A productive and effective path forward to test new drugs efficiently for AS will require alignment of multiple stakeholders; clarity and agreement on the relevant goalposts for approval; development of a clinical trial network with standardized imaging protocols and end point assessment; and the focus, resolve, and creativity to tackle and to solve the challenges that arise. Recent and ongoing advances in elucidating the pathobiology of AS have identified numerous promising targets and existing therapies to test. A fit-for-purpose infrastructure and overarching plan now needs to be built and executed to evaluate these potential therapies for the betterment of the millions of individuals who now have or will develop AS (**Central Illustration**). To that end, we propose that a multistakeholder working group be convened including experts in valvular heart disease and representatives from National Institutes of Health, Centers for Medicare and Medicaid Services, FDA, industry, Heart Failure Collaboratory, patient advocacy groups, and others under the auspices of the Heart Valve Collaboratory to provide forward momentum for the ambitious goal of launching a clinical trials research network that could execute a platform trial as proposed to move the field from promising targets to proven therapies.

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KEY WORDS aortic valve stenosis, computed tomography, echocardiography, medical therapy, randomized clinical trial, trial endpoints, valvular heart disease

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APPENDIX For a supplemental table, please see the online version of this paper.