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Supplementary appendix

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Supplementary Table 1. AI-augmented screening tools for valvular heart diseases

Digital tool	Valvular Heart Disease	Training Cohort	Validation Cohort	AUC	Sensitivity	Specificity
AI-augmented auscultation tool						
Ghanayim et al[1] (2022)	Mod or Severe AS	100	External validation (n=106)	-	90%	84%
Chorba et al[2] (2021)	Moderate or Severe AS	5878 audio recordings, from 5318 patients	External validation at 4 sites (954)	0.95	93.2%	86%
	Moderate or Severe MR			0.865	66.2%	94.6%
AI-augmented ECG						
Kwon et al[3] (2020)	Moderate or severe AS	25,733	External validation at a single site (n = 10,865)	0.86	80%	78.3%
Kwon et al[4] (2020)	Moderate or severe MR	24,202	External validation at a single site (n = 10,865)	0.88	90%	67%
Cohen-Shelly, et al[5] (2021)	Moderate to severe AS	129,778	No external validation Development and validation cohorts from same sites (n = 102,926 across 4 hospitals)	0.85	78%	74.3
Ulloa-Cerna et al[6] (2022)	Moderate to severe VHD (AS, AR, MS, MR, and TR)	332,919	External validation at 11 sites (n = 315,863)	0.91	90%	72%
Elias et al[7] (2022)	Moderate to severe valvular disease (AS, AR, MS, and MR)	43,165	Internal validation (n= 21,048)	0.84	78%	73%
			External validation at a single site (n = 3,194)	0.76	-	-
Sawano et al[8] (2022)	Moderate or severe AR	18,954	Internal validation (n=3,269)	0.80 (multi-input model)	53.5%	82.8%
Vaid et al[9] (2023)	Moderate-to-severe or Severe MR	116,612 (MR)	No external validation External validation (MR) (n=8604)	0.81	83%	63%
	Moderate-to-severe or Severe AS	120,564 (AS)	(AS) (n=8171)	0.86	92%	63%

AI, artificial intelligence; AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; TR, tricuspid regurgitation; AUC, area under the receiver operator characteristic curve

Supplementary Table 2. Pharmacotherapy Clinical Trials in Aortic Stenosis

Previous clinical trials

- Statin trials to reduce low-density lipoprotein cholesterol have failed to demonstrate any benefit in delaying the progression of AS [10].
- RANKL inhibitor, denosumab, and bisphosphonate, alendronic acid, did not prove to be effective in slowing down the process of calcific AS in the SALTIRE 2 trial [11].
- Menaquinone-7 (MK-7), also known as vitamin K2, is a cofactor for the carboxylation of proteins involved in inhibiting arterial calcification and was tested along with vitamin D against a placebo [12]. The progression of the aortic calcification score was not significantly different between patients treated with MK-7 plus vitamin D and patients receiving a placebo.
- A small trial of an aldosterone antagonist, eplerenone, showed no reduction in AS progression [13].

Ongoing Clinical trials

- The BICATOR trial (NCT02679261) has completed enrolling 220 patients to evaluate the effect of atorvastatin in reducing the progression of aortic dilation in patients with BAV. The progression of aortic valve calcification is the trial's secondary end-point in a three-year follow-up period [14].
- Early Aortic Valve Lipoprotein(a) Lowering Trial [EAVaLL (NCT02109614)] is being conducted to test whether the reduction of Lp(a) by Niacin can reduce the progression of calcific AS. Recruitment (n=238) for this trial has begun in individuals with aortic sclerosis or mild AS (aortic valve area [AVA] >1.5 cm^2, mean gradient [MG] < 25 mmHG) and high Lp(a) [15].
- A randomized trial is testing a PCSK-9 inhibitor in 140 patients using CT and NF-PET as imaging end-point [16].
- Ataciguat is NO-independent sGC activator. The safety and effects of ataciguat are currently being assessed in two studies involving patients with mild to moderate calcific AS. [(NCT02049203) and (NCT02481258] [17,18].
- EVOID-AS trial (NCT05143177) is a phase 2/3 multicenter double-randomized clinical trial to test whether Evogliptin can reduce the calcification of the aortic valve and reduce the hemodynamic progression of AS after a two-year follow-up in 867 patients using three-arm intervention (Evogliptin 5 mg, Evogliptin 10 mg, and placebo) in the United States [19].
- Lp(a)FRONTIERS CAVS (NCT05646381) is a randomized double-blind, placebo-controlled, multicenter trial assessing the impact of lipoprotein(a) lowering with Pelacarsen on the hemodynamic progression of calcific AS in 502 patients followed up over 3 years [20].

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