Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Contents

1. Supplementary Table 1 ........................................ 1
2. Supplementary Table 2 ........................................ 2
3. References .................................................... 3-4
Supplementary Table 1. AI-augmented screening tools for valvular heart diseases

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

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 \(^{20}\).
References

14. Evaluating the Effectiveness of Atorvastatin on the Progression of Aortic Dilatation and Valvular Degeneration in Patients With Bicuspid Aortic Valve. [https://ClinicalTrials.gov/show/NCT02679261](https://ClinicalTrials.gov/show/NCT02679261).
15. Early Aortic Valve Lipoprotein(a) Lowering Trial. [https://ClinicalTrials.gov/show/NCT02109614](https://ClinicalTrials.gov/show/NCT02109614).
16. PCSK9 Inhibitors in the Progression of Aortic Stenosis. [https://ClinicalTrials.gov/show/NCT03051360](https://ClinicalTrials.gov/show/NCT03051360).
17. Safety of Ataciguat in Patients With Moderate Calcific Aortic Valve Stenosis. [https://ClinicalTrials.gov/show/NCT02049203](https://ClinicalTrials.gov/show/NCT02049203).
18. A Study Evaluating the Effects of Ataciguat (HMR1766) on Aortic Valve Calcification. [https://ClinicalTrials.gov/show/NCT02481258](https://ClinicalTrials.gov/show/NCT02481258).