EUROVALVE

DEBATING CHAMBER

CAMBRIDGE UNION SOCIETY

OCTOBER 7&8,2022

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FACULTY DISCLOSURE

I have no financial relationships to disclose

That this House believes

AS may be treated by preventing aortic valve calcification

Proposition: Cécile Oury, GIGA-Cardiovascular Sciences, University of Liège, Belgium

Expert panel : Marc Dweck, Benoy Shah

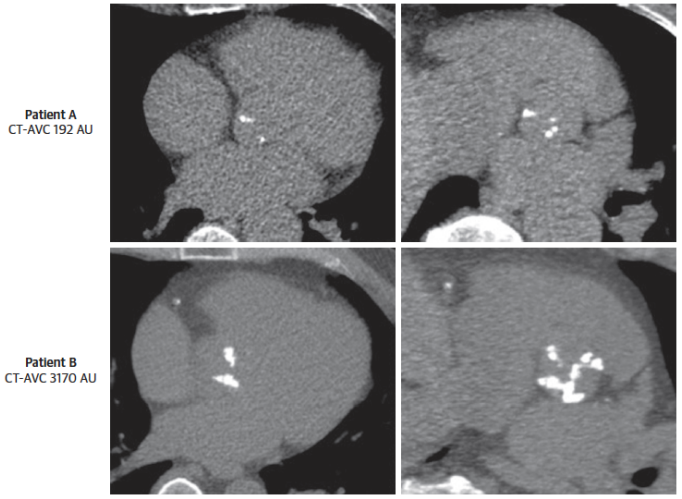
I. **RATIONALE**

II. CHALLENGES

III. SOLUTIONS

IV. CONCLUSIONS

1. AVC DRIVES AS AND IS ASSOCIATED WITH POOR OUTCOME



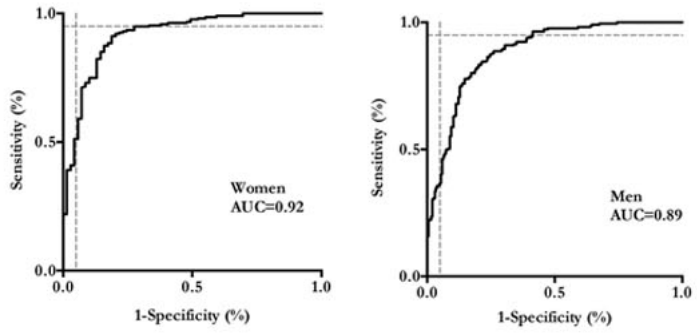
Doris et al. J Am Coll Cardiol Img. 2019

Non-contrast electrocardiogram-gated computed tomography
→ aortic valve calcium scoring (CT-AVC):

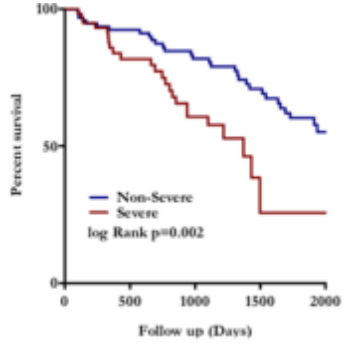
Sex-specific CT-AVC thresholds (1377 Agatston unit in women and 2062 Agatston unit in men) are independent predictors of aortic valve replacement and death

Also in patients with discordant echocardiographic markers of AS severity

Diagnostic accuracy for severe AS

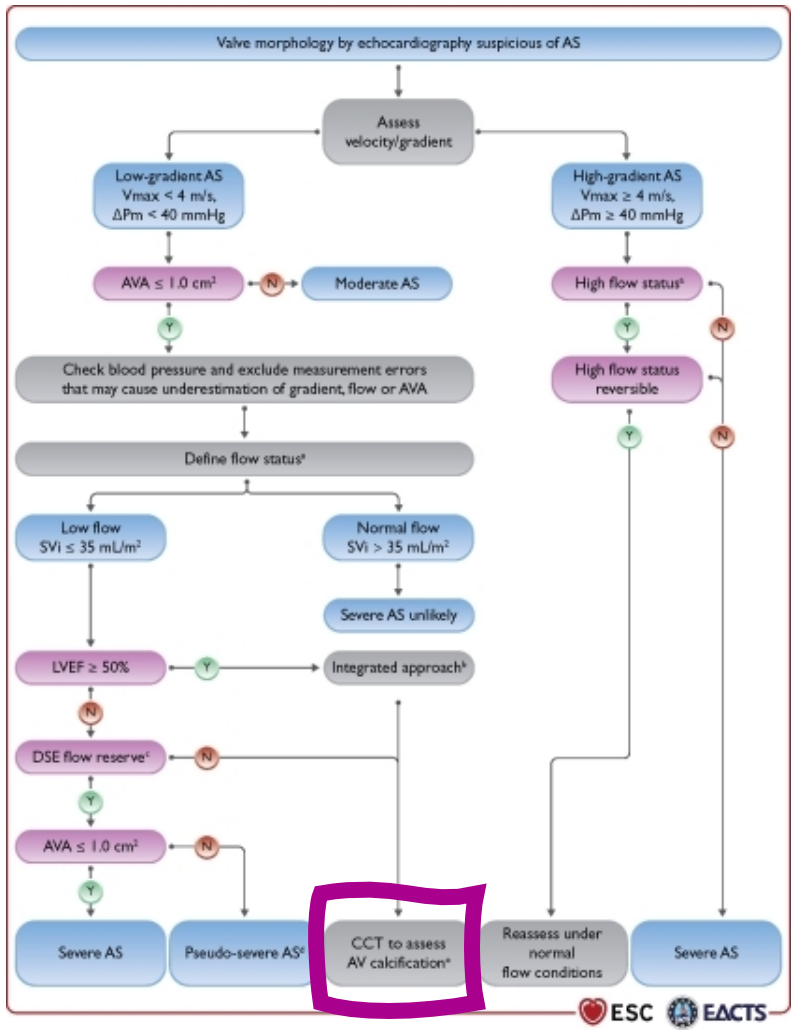


Risk stratification



Clavel et al. J Am Coll Cardiol 2014; Pawade et al. Circulation: Cardiovascular Imaging. 2018; Pawade et al. J Am Coll Cardiol Img. 2019

2021 ESC/EACTS Guidelines for the management of valvular heart disease



« Quantification of valve calcification predicts disease progression and clinical events and may be useful when combined with geometric assessment of valve area in assessing the severity of aortic stenosis in patients with low valve gradient. »

Severe AS: men >3000, women >1600 = highly likely; men >2000, women >1200 = likely; men <1600, women <800 = unlikely

Vahanian et al. Eur Heart J 2021

2. AVC PROPAGATION DOES NOT DEPEND ON ATHEROSCLEROTIC RISK FACTORS

- AVC is progressive, appearing de novo with progressive atherosclerosis (determined by high LDL-c)
- **Established AVC progresses independently of atherosclerotic risk factors and faster with higher initial AVC loads**

→ Distinct sets of factors likely contributes to AVC propagation → Need for distinct treatments

Messika-Zeitoun et al. Ateroscler Thromb Vasc Biol. 2007

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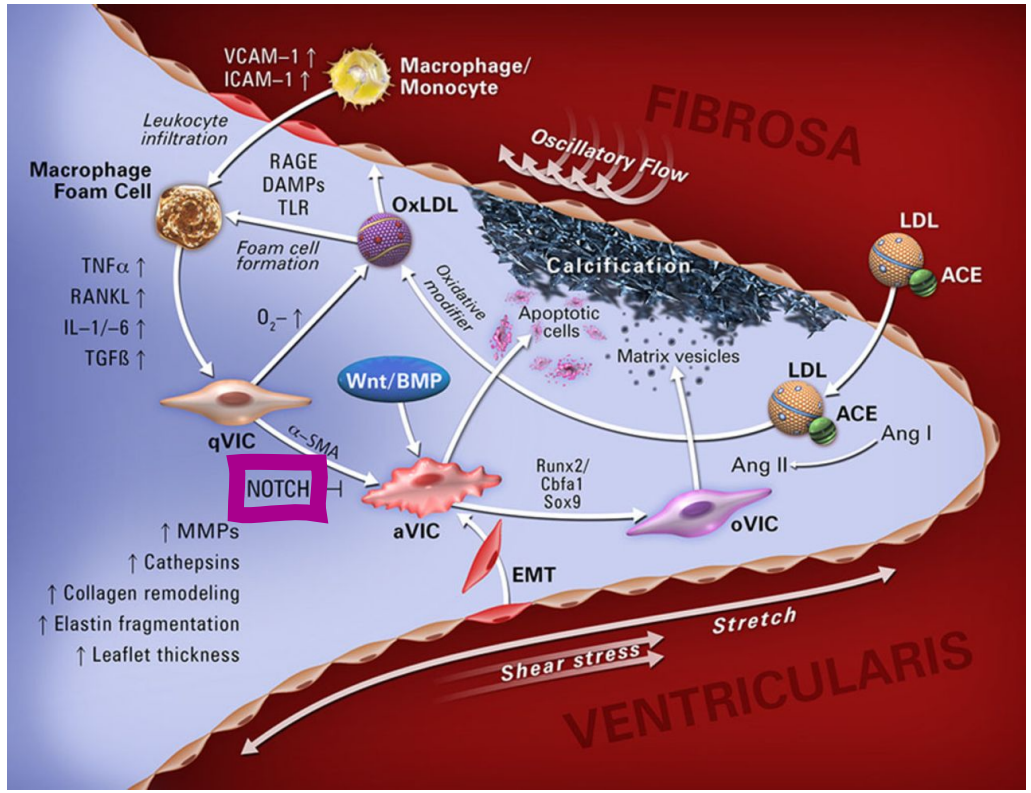
AVC PATHOPHYSIOLOGY: A COMPLEX TWO-PHASE PROCESS



Histopathologic heterogeneity

Amorphous calcium phosphate deposits (epitaxial mineral deposition on cholesterol crystals, fragmented elastin fibers, collagen)
AND
Ectopic bone formation (transformation of VIC)

Several cellular and molecular mechanisms converge to regulate AVC load

Different mechanisms for initiation and propagation

Towler DA. Circ Res. 2013; Yutzey et al. Arterioscler Thromb Vasc Biol 2014

LDL-C *versus* Lp(a) lowering drugs in AS

2022 EAS Consensus on Lp(a)

LDL-Cholesterol (LDL-C)

Observational evidence

- LDL-C associated with incident aortic stenosis
- Genetic LDL-C risk score supported causality

Interventional trial evidence with statins

No benefit by LDL-C lowering

Discussed reasons

- Amount of LDL-C lowering insufficient
- LDL-C lowering too short
- LDL-C involved in initiation but not progression of the disease
- Off-target effects of statins including pro-osteogenic properties, worsening of insulin resistance or increased Lp(a)

Lipoprotein(a) [Lp(a)] + oxidized phospholipids

Observational evidence

- Strong association between high Lp(a) and aortic stenosis
- Pronounced genetic support for causality
- Unclear whether high Lp(a) is associated with progression or only with initiation but not with progression of aortic stenosis

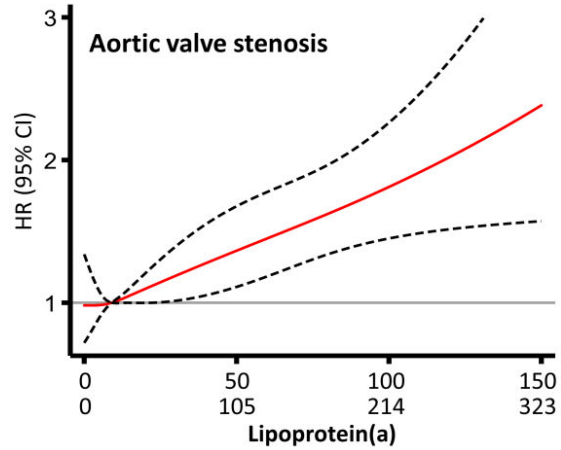
Questions concerning trial planning

Inclusion criteria

- With or without signs of calcification/aortic stenosis at baseline?
- How high should Lp(a) be for inclusion?

Endpoint

- Aortic valve replacement
- Development and/or progression of calcification



High Lp(a):

- Associated with both micro- and macrocalcification
- Promotes faster AS progression (AVR/death)

Kronenberg F. Eur Heart J 2022

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- **Promise of Lp(a) lowering**
- **Targeting key biological pathways responsible for AVC propagation**

Nitric oxide-NOTCH1

- Valvular endothelia play a protective role against AVC
- VEC-derived NO activates NOTCH1 signaling
- Mutations in *NOTCH1* are associated with bicuspid aortic valve and calcific AS

Garg et al., Nature 2005; Bosse et al. J. Mol. Cell. Cardiol 2013

Nitric oxide-NOTCH1

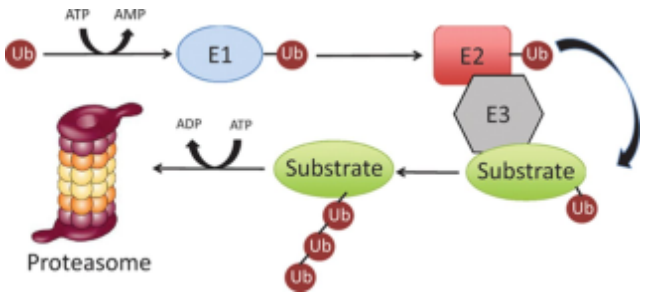
Richards et al., Am J Pathol. 2013

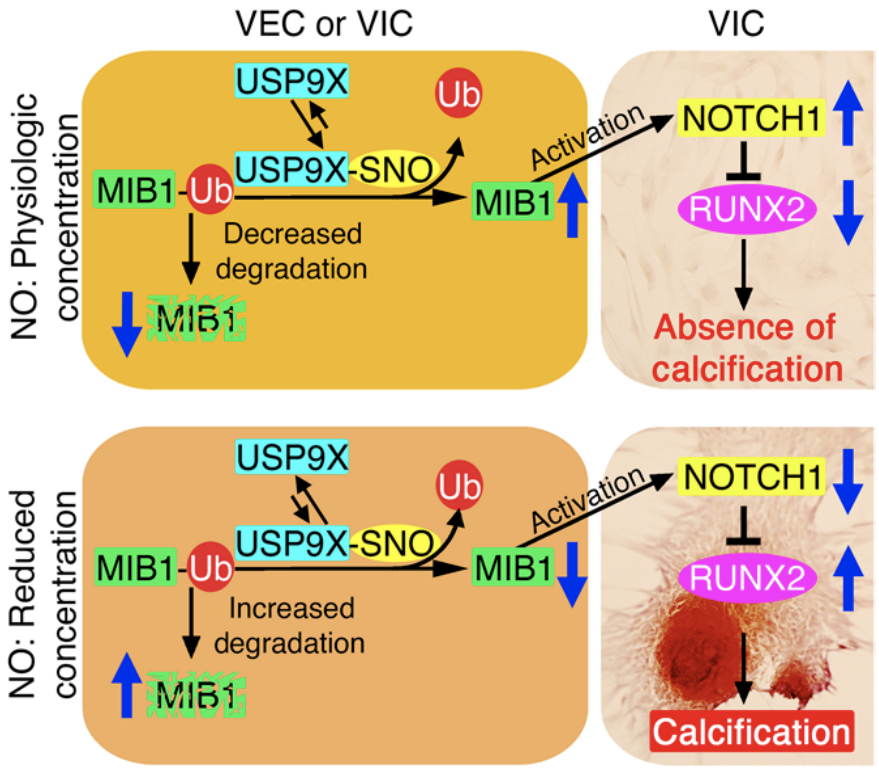
Majumdar et al., Sci. Adv. 2021

Science Advances | AAAS
SIGNIFICANT RESEARCH, GLOBAL IMPACT

Nitric oxide-NOTCH1-UPS

Ubiquitin-proteasome system



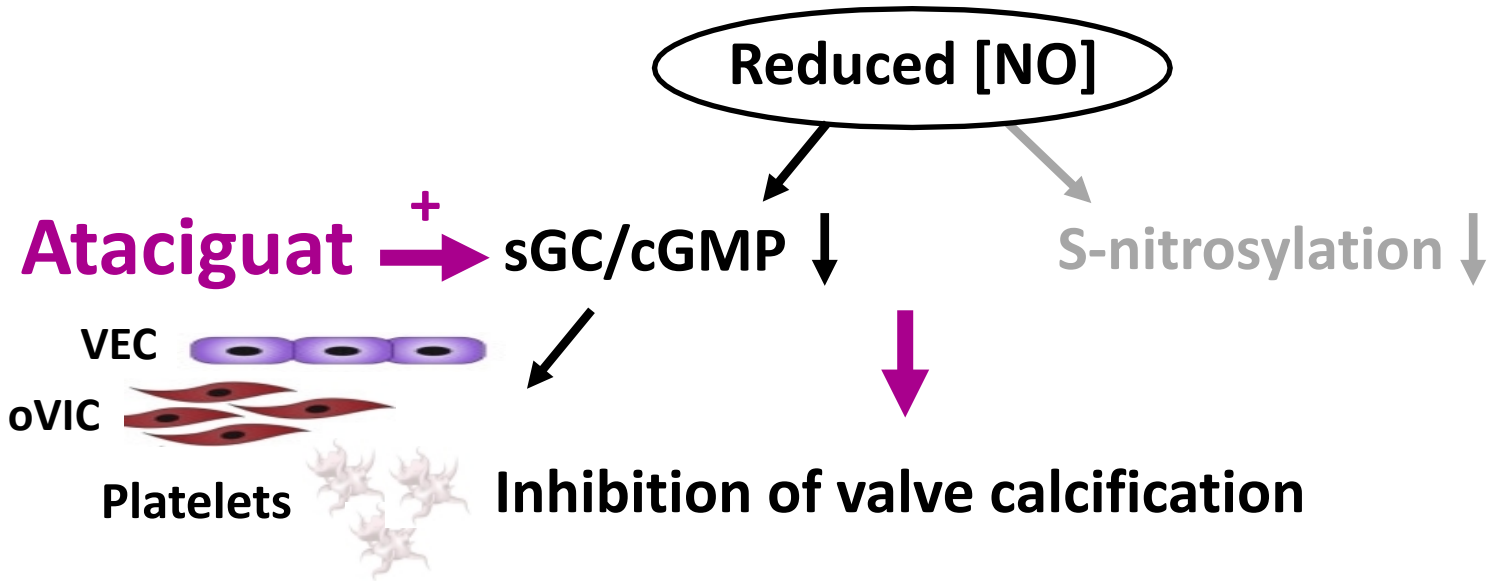


- Mice with endothelial-specific deletion of USP9X develop AS
- Reduced USPX9 S-nitrosylation in human calcified AoV

→ **NO pathway activators and regulators of the ubiquitin-proteasome system: potential therapeutic targets in AVC**

Majumdar et al., Sci. Adv. 2021

NO pathway activators



ONGOING CLINICAL TRIAL (NCT02481258)

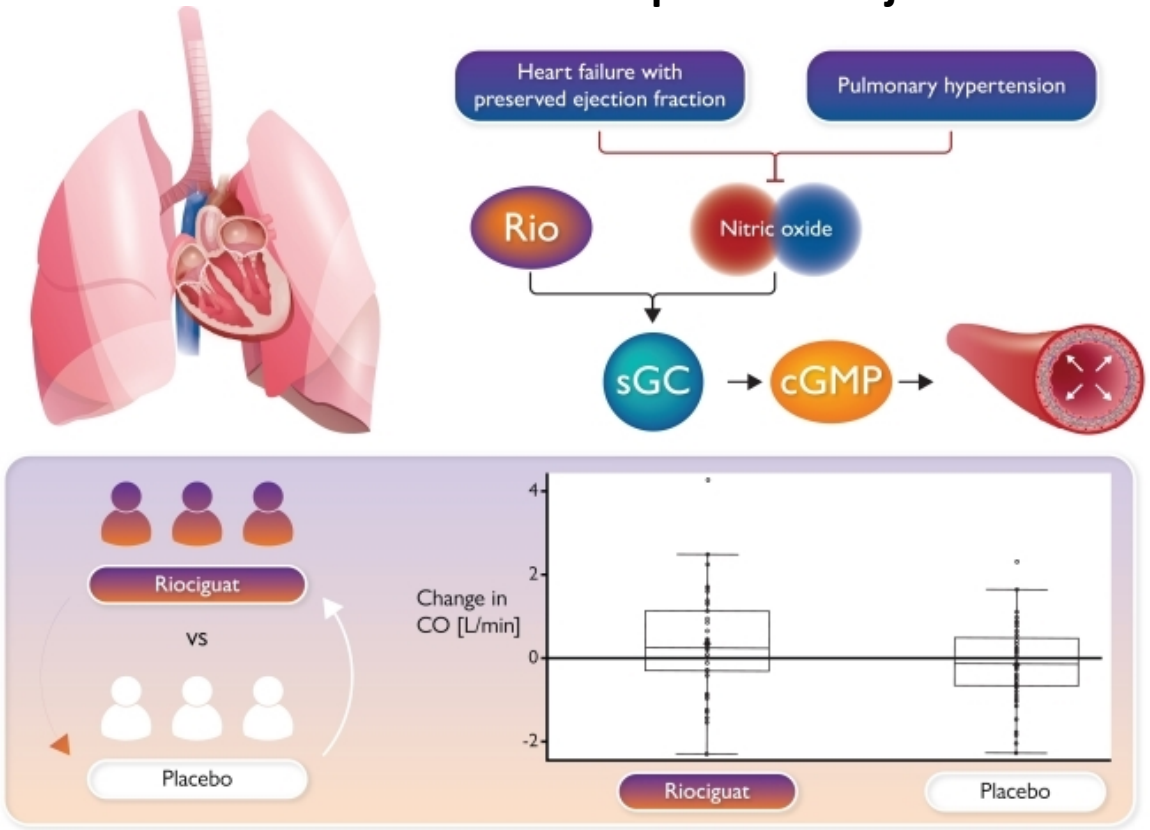
Abstract: Patients with mild-to-moderate CAVS were treated with placebo or Ataciguat (200 mg/day) for 6 months showed decreased progression of AVC

Zhang et al., Arterioscler Thromb Vasc Biol 2019

NO pathway activators: HFpEF and PH

ESC European Society of Cardiology

Riociguat in pulmonary hypertension and heart failure with preserved ejection fraction: the haemoDYNAMIC trial



- Vasodilatation
- Anti-inflammatory
- Anti-fibrotic
- Anti-thrombotic

Dach et al. Eur Heart J, 21 September

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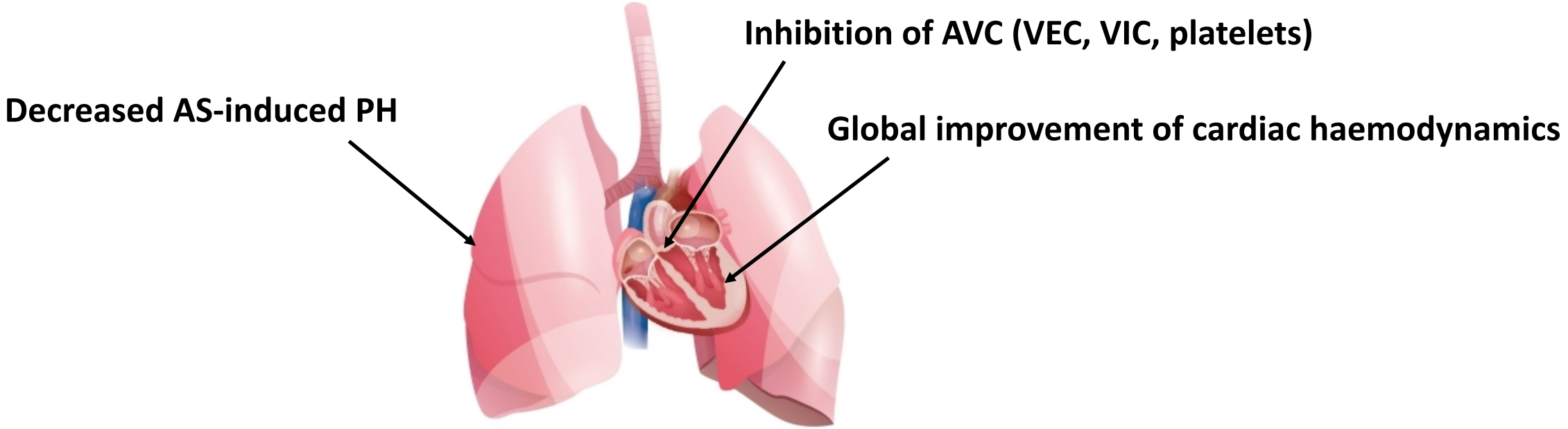
AS may be treated by preventing aortic valve calcification propagation

Targeting the NO pathway may represent a valuable treatment in AS



Thank you for your attention