European Heart Journal (2025) 46 (Suppl 1)
Basic Science – Cardiac Diseases, Valvular Heart Disease

Prevention of aortic valve stenosis through modulation of LXRb using saringosterol

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Funding Acknowledgements: Type of funding sources: Public grant(s) – National budget only. Main funding source(s): TRR259 BONFOR

Background: The liver X receptor-beta (LXRβ) is a regulator of inflammation and cellular cholesterol metabolism. Saringosterol is a ligand of LXR. Both, inflammation and lipid dysregulation promote calcific aortic valve stenosis (AS). Whether saringosterol alleviates AS through LXR signalling is unknown.

Aim: Our aim was to assess the effect of saringosterol on AS.

Methods: To test the relevance of LXR for AS, aortic valve tissue samples from patients with AS were compared to non-stenotic controls using transcriptome analysis.

In vitro, human aortic valve interstitial cells (VICs) were stimulated with saringosterol under pro-calcifying conditions or co-incubated with cholesterol to assess effects on cellular cholesterol metabolism, cholesterol efflux, cell differentiation, and inflammatory pathways. Gene expression was measured using real-time PCR.

Mice were fed a saringosterol-enriched diet. AS was induced applying the microsurgical wire injury model. AS was quantified using echocardiography and subsequent histology. Sterol concentrations in the liver, bile, and plasma were measured by gas chromatography-mass spectrometry with selected ion monitoring. The expression of LXRβ-regulated genes in tissue samples was analysed by real-time PCR.

Results: In human valve tissue, transcriptome analysis revealed that various GO terms related to LXRβ in AS are differentially regulated, such as GO:0046890 - Regulation of the lipid biosynthesis process.

In vitro, saringosterol treatment resulted in a significant, dose-dependent induction of ABCA1 and ABCG1. In contrast, saringosterol significantly reduced the expression of markers for osteoblastic differentiation (RUNX-2) and myofibroblastic differentiation (ACTA-2). In addition, the expression of IL-1β was reduced.

In vivo, oral administration of saringosterol induced LXR target genes in the liver and the intestine. AS was significantly attenuated by oral administration of saringosterol. Consistently, the histologically measured valve area was also significantly smaller.

Conclusion: In the present study, transcriptome analysis suggests a central role of the LXRβ in human AS. The LXR-ligand saringosterol improves cellular cholesterol efflux in VIC while reducing unwanted cell differentiation and inflammation. In vivo, oral administration of saringosterol induces LXRβ target genes and mitigates AS.