Letter to the Editors

The leukotriene receptor antagonist montelukast and aortic stenosis

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Aortic stenosis shares several characteristics with atherosclerotic lesions, such as inflammation and lipid accumulation leading to extensive calcification of the valvular leaflets, which eventually causes the aortic valve to narrow [1]. However, lipid lowering drugs of the statin class have not been shown to retard the progression of aortic stenosis. In fact, to date there is no medical treatment for this valvular heart disease and aortic stenosis remains the most common indication for surgical valve replacement [1].

Recently, the leukotriene pathway was shown to be associated with aortic stenosis. Local leukotriene production in calcified human valves increased reactive oxygen species production, activated osteogenic pathways and stimulated calcification [2]. In addition, the expression levels of leukotriene synthesizing enzymes within aortic valves were significantly correlated with the severity of aortic stenosis, as determined by echocardiography [2]. Leukotriene receptor antagonists (LTRA) are a well-established treatment of asthma. In addition, we recently showed that the therapeutic potential of anti-leukotriene drugs may go beyond asthma, based on the observation that the LTRA montelukast was associated with a decreased risk for recurrent cardiovascular events, such as stroke and myocardial infarction [3].

Taken together, these observations suggested that LTRAs may be protective for the development of aortic stenosis. To test this hypothesis, we have analyzed the incidence of aortic stenosis in relation to the use of montelukast. In brief, a nationwide population-based cohort of approximately 7 million Swedish residents integrating data from the Prescribed Drug, Patient, Cause of Death, Income, Educational and Emigration Registers was followed from July 1 2005, to December 31 2008. The cohort and statistical methods have been described in detail in our previous studies [3, 4]. Analyses were performed in the whole adult population after exclusion of subjects with a

prior diagnosis of aortic valve disease (ICD-10 code I35; ICD-9 code 4241; ICD-8 code 3659 and 4241).

Montelukast exposure was defined from the national Swedish Prescribed Drug Register as claimed prescriptions of Anatomical Therapeutic Chemical (ATC) code R03DC03. Calculated from each dispense date, subjects were considered exposed for 3 months based on a prescription length of 3 months of use. Aortic stenosis (ICD-10 codes I35.0 and I35.2) was monitored as outcome and defined according to either the primary diagnosis or the primary cause of death, as recorded in the Patient and Cause of Death Registers. The associations between montelukast use and outcome were examined by Cox proportional hazard models estimating the hazard ratio (HR) of drug use, after adjustment for age, gender and socioeconomic factors (education level and income), the presence of respiratory disease and the use of drugs for respiratory and cardiovascular disease, as previously described [3] and detailed in supplementary Table S1.

The prevalence of aortic valve disease in the whole population was 0.25% at baseline. Montelukast use was associated with a trend of decreased incidence of aortic stenosis, which did not reach statistical significance (Table 1).

Several limitations of the present study should be acknowledged. The 3.5 years of exposure data available in the present study is relatively short given that aortic stenosis develops over a longer time. It can also not be excluded

Table 1

Fully adjusted* hazard ratio (HR) with 95% confidence interval (95% CI) for aortic stenosis with montelukast (non-use was used as reference level)

Number of events	Event rate (per 1000 PYAR)	HR (95% CI)
10 983	0.44 (0.44, 0.45)	0.81 (0.57, 1.16)

*Adjusted for all parameters listed in Supplementary Table 1. PYAR, person-years at risk.

*Both authors contributed equally to this study.

that previously exposed subjects may have been considered as unexposed, and that recently commenced montelukast treatment may not yet have affected the development of aortic stenosis. In addition, using the diagnosis code as outcome will not define the severity of aortic stenosis and will miss asymptomatic cases not seeking hospital care. The latter limitations can drive the association towards the null due to lower statistical power. Finally, in these national registry data, we are not able to adjust completely for all possible confounding factors. However, the most plausible confounders have been taken into account by adjustment for gender, age, socioeconomic status as well as cardiovascular and respiratory diagnoses and treatments.

In summary, mechanistic studies have implicated the leukotriene pathway in aortic stenosis. Although the present study did not show a significant association of montelukast use with aortic stenosis, the results suggested a trend towards beneficial effects. However, the non-randomized, observational design of the present study means that no causality can be definitely attributed and that the association could be driven by unmeasured confounding. More importantly, the present study indicates a safety of anti-leukotriene drugs in the context of aortic stenosis. The latter finding is an important piece of information for the design of interventional studies targeting the leukotriene pathway in aortic stenosis.

Competing Interests

There are no competing interests to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1

Baseline characteristics of the study sample