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Metabolic risk markers and relative survival in patients with aortic stenosis requiring surgery.

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorexamen framläggs till offentligt försvar i sal B, Unod T, 9tr, Norrlands Universitetssjukhus fredagen den 14 juni, kl. 13:00.

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Author: Anders Holmgren**Title: Metabolic risk markers and relative survival in patients with aortic stenosis requiring surgery****Abstract**

Background: Aortic stenosis (AS) is the most common valve disorder requiring surgery in developed countries. The etiology of AS is only partly known. Identification of new biomarkers in prospective studies could lead to novel insights in the etiology of AS, and possibly lead to improved clinical management. Long term observed survival after aortic valve surgery has improved over the last decades despite an ageing population presenting with more comorbidities. Whether this is reflected in improved relative survival is not known. We evaluated if biomarkers associated prospectively with AS requiring surgery, and if these associations differed between genders, time to surgery and the presence of coronary artery disease (CAD). We also assessed long term observed and relative survival after aortic valve surgery with and without concomitant coronary artery by-pass surgery (CABG).

Methods and results: Study I: We prospectively studied the impact of lipoprotein (a) (Lp[a]) and apolipoproteins (Apo) in subgroups of AS. During a 20-year period 336 patients with prior participation in large population-based surveys in northern Sweden were operated due to AS plus CABG when indicated. For each case two referents were matched. Data from the baseline survey were collected and included data on cardiovascular risk factors, health history, measurements of anthropometry, blood pressure, blood glucose and blood lipid levels were retrieved. Data from pre- and perioperative assessments were also collected. The presence of CAD was determined from the coronary angiogram. Elevated levels of Lp(a) and an elevated Apo B/Apo A 1 ratio were independently associated with future surgery for AS, but only in patients with concomitant CAD (OR 1.29, 95 % CI 1.07-1.55 and 1.43, 95 % CI 1.16-1.76 respectively). **Study II:** The same patient cohort as in study I was used. A panel of 92 cardiovascular candidate proteins were analysed with the multiplex proximity extension assay in samples obtained at baseline. Six circulating proteins (growth differentiation factor 15[GDF-15], galectin-4, von Willebrand factor [vWF], interleukin 17 receptor A, transferrin receptor protein 1, and proprotein convertase subtilisin/kexin type 9, [PCSK9]) were associated with future surgery for AS in patients with concurrent CAD (ORs ranged from 1.25 to 1.37 per SD increase in the protein signal). In the validation study with 106 additional cases, the association of all but one, (interleukin 17 receptor A), of these proteins were replicated in patients with AS and concurrent CAD but not in those without concurrent CAD. **Study III:** In the same patient cohort as in study I and II we evaluated if troponin T (TnT) and C-reactive protein (CRP) associated prospectively with future surgery for AS. TnT was independently associated with surgery for AS in patients both with (OR 1.22, 95 % CI 1.02-1.46) and without concomitant CAD (1.39, 95 % CI 1.05-1.84). CRP was not associated with surgery for AS (OR 1.06, 95 % CI 0.92-1.23). **Study IV:** 4970 patients between 2005 and 2016 from three Swedish heart surgery centres, undergoing aortic valve replacement (AVR) due to either AS or aortic regurgitation in conjunction with CABG when indicated, were followed up. All-cause mortality, as well as both observed and relative survival, was analysed with focus on age, sex, type of valve prosthesis and the impact of concomitant CABG. Median follow-up was 4.7 years (2.3-7.6). 30-day mortality was 2.3 %. Long-term survival with 30-day mortality excluded was 96.6 %, 82.7 %, 57.6 % after 1, 5 and 10 years respectively. Relative survival rates (adjusting for the background mortality in the general Swedish population based on age, sex and year) were 99.6 %, 99.5 % and 90.6 % after 1, 5 and 10 years respectively. Age had a negative influence on observed survival ($p < 0.001$) but was associated with better relative survival (relative mortality rate [RMR] 0.74, 95 % CI 0.71 - 0.77). Women had a lower observed mortality than men ($p < 0.001$) but a lower relative survival (RMR 1.17, 95 % CI 1.02-1.35). Combined surgery (AVR+CABG) was not significantly associated with higher mortality ($p = 0.43$) in a multivariable adjusted analysis. The presence of bicuspid morphology was associated with lower observed mortality compared with tricuspid valve, and a relative survival matching that in the general population.

Conclusion: I. Plasma levels of Lp(a) and the Apo B/Apo A 1 ratio were independently associated with future surgery for AS but only in patients with concomitant CAD. This finding suggests that patients with AS have different phenotypes and may open a new avenue of research on targeted risk factor interventions in this population. **II.** Five circulating proteins – GDF-15, galectin-4, vWF, transferrin receptor protein 1, and PCSK9 – were associated with the need for aortic valve surgery several years later. The role of these proteins should be investigated in future studies. **III.** Elevated plasma levels of TnT were independently associated with future surgery for AS, irrespective of the presence of concomitant CAD, which could indicate that the myocardium is subject to mechanical stress already in the subclinical stage of AS. This may be used as a clinical tool for identification of patients with subclinical AS who could benefit from early intervention. Elevated CRP levels did not associate with future AVR. **IV.** Relative survival following AVR was particularly good in the elderly matching that in the general population underlining the benefits of aortic valve surgery in properly selected patients. Women had decreased relative survival compared to men. This should be explored in future studies. Adding CABG to an AVR procedure was not associated with increased risk. Bicuspid valve morphology was associated with lower observed mortality compared with tricuspid valve morphology, and with a relative survival matching that of the general population.

Keywords: Aortic stenosis, aortic valve surgery, coronary artery disease, prospective cohort study, risk markers, lipoprotein (a), apolipoproteins, proteomics, troponin T, C-reactive protein, relative survival, observed survival

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