

Cardiovascular outcomes and extra-articular manifestations in patients with spondyloarthritis

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i föreläsningssalen våning 3, Guldhedsgatan 10A, Göteborg, fredagen den 20 mars, klockan 09.00

av **Karin Bengtsson**

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Avhandlingen baseras på följande delarbeten

- I. Bengtsson K, Forsblad-d'Elia H, Lie E, Klingberg E, Dehlin M, Exarchou S, Lindström U, Askling J, Jacobsson LTH. Are ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis associated with an increased risk of cardiovascular events? A prospective nationwide population-based cohort study. *Arthritis Research and Therapy* 2017; 19:102.
- II. Bengtsson K, Forsblad-d'Elia H, Lie E, Klingberg E, Dehlin M, Exarchou S, Lindström U, Askling J, Jacobsson LTH. Risk of cardiac rhythm disturbances and aortic regurgitation in different spondyloarthritis subtypes in comparison with general population: a register-based study from Sweden. *Annals of the Rheumatic Diseases* 2018; 77: 541-8.
- III. Bengtsson K, Klingberg E, Deminger A, Wallberg H, Jacobsson LTH, Bergfeldt L, Forsblad-d'Elia H. Cardiac conduction disturbances in patients with ankylosing spondylitis: results from a 5-year follow-up cohort study. *RMD Open* 2019; 5(2):e001053.
- IV. Bengtsson K, Forsblad-d'Elia H, Deminger A, Klingberg E, Dehlin M, Exarchou S, Lindström U, Askling J, Jacobsson LTH. Incidence of extra-articular manifestations in ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis – results from a national register-based cohort study. *Manuscript*.

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ABSTRACT

Background: Spondyloarthritis (SpA) is a cluster of rheumatic diseases with similar clinical features, including association with extra-articular manifestations such as anterior uveitis (AU), inflammatory bowel disease (IBD) and psoriasis. Ankylosing spondylitis (AS), psoriatic arthritis (PsA) and undifferentiated SpA (uSpA) are the major subtypes of SpA. Chronic inflammatory diseases are potential risk factors for cardiovascular disease (CVD). The risk of CVD events in the different SpA subtypes has not been analysed in the same setting in large populations. Further, SpA has been linked to specific cardiovascular manifestations such as aortic regurgitation and cardiac conduction disturbances (CCDs).

Objectives: The aims with this thesis were to: A) calculate the incidence of acute coronary syndrome (ACS), stroke, venous thromboembolism (VTE), cardiac rhythm disturbances, aortic regurgitation, AU, IBD and psoriasis in patients with AS, PsA and uSpA in comparison to each other and to controls from general population (GP), B) describe electrocardiographic (ECG) development in AS and to identify associations between baseline characteristics and CCDs at five-year follow-up.

Methods: A) Cohorts of patients and controls from GP were identified and followed prospectively through a nationwide and comprehensive linkage of the Swedish health care and population registers. Incidence rates (IRs), events per 1000 person-years at risk, were calculated and standardized to the age and sex distribution in GP. For comparison of the cohorts, Cox regression, with age/sex-adjusted hazard ratios (HRs), and Poisson regression, with incidence rate ratios (IRRs), analyses were performed. B) A longitudinal cohort study of 172 patients with AS examined with ECG in 2009 and after five year in 2014. Logistic regression analyses were performed to identify if baseline characteristics were associated with a CCD at five-year follow-up.

Results: A significantly increased risk of all studied cardiovascular outcomes was demonstrated in SpA in comparison to GP. For ACS, stroke and VTE, the age/sex-adjusted HR point estimates in the SpA subtypes ranged between 1.4 to 1.8, 1.2 to 1.3 and 1.5 to 1.5, respectively. The increased relative risk of ACS was especially pronounced in women with PsA (age-adjusted HR 2.0). Regarding cardiac rhythm disturbances, the highest absolute risk (IRs) was noted for atrial fibrillation (5.5 to 7.4 events per 1000 person-years), whereas the highest relative risk vs GP was found for AV block II-III in men with uSpA (age-adjusted HR 4.2) and AS (age-adjusted HR 2.5). In patients with AS, uSpA and PsA vs matched controls, relative risks (IRRs) were significantly increased for AU (20.2, 13.6 and 2.5), IBD (6.2, 5.7 and 2.3) and psoriasis (2.5, 3.8 and not applicable). In the ECG study, 13% had a CCD at follow-up. In age/sex-adjusted analyses; CCD at baseline, male sex, history of AU, higher AS disease activity score based on CRP, greater waist circumference, medication with anti-platelets and beta-blockers were associated with a CCD at five-year follow-up. Higher age/longer AS symptom duration was also associated with a CCD.

Conclusions: Patients with SpA have an increased risk of different manifestations of CVD including ACS and stroke in comparison to general population. These results underscore the need to implement strategies to improve CVD risk factors management in clinical practice for patients with SpA irrespective of subtype. Further, AS characteristics as well as markers of CVD were associated with the presence of CCD. Last, a strong association for AU and IBD was noted in AS, closely followed by uSpA, whereas the association for these manifestations was considerably weaker in PsA.

Keywords: Spondyloarthritis, cardiovascular disease, extra-articular manifestations