Spinal fractures related to ankylosing spondylitis

Epidemiology, clinical outcome and biomechanics

YOHAN ROBINSON
Abstract

Background: Spinal fractures related to ankylosing spondylitis (AS) are often associated with serious complications. Therefore, knowledge of the incidence, best treatment, outcome, and prevention would assist in improving current guidelines.

Objectives: This thesis aims at (1) analysing the complications and mortality of surgical treatment, (2) mapping the incidence and treatment modalities for these patients in Sweden, as well as (3) investigating the putative preventive effect of biological disease modifying anti-rheumatic drug (bDMARD) therapy on spinal fractures related to AS.

Methods: Merged multiple national registries were used to identify predictors of mortality and spinal fractures in patients with AS. Beyond that a finite element model (FEM) was designed to simulating a cervicothoracic fracture related to AS.

Results and Conclusions: During the last two decades an increase of the incidence of vertebral fractures in patients with AS was observed. With the introduction of bDMARD treatment of AS was revolutionised and quality of life and function improved. It seems that the improved quality of life and function in these patients does not correlate with a reduced fracture risk. Still, for the first time a beneficial effect of bDMARD with regard to spinal fracture occurrence was provided. The risk of spinal fractures was not reduced, but the debut of a spinal fracture was delayed with bDMARD. Since for this study the observation interval was only a decade, a future follow-up should revisit the effect of bDMARD on spinal fractures related to AS.

Furthermore, it was shown that posterior stabilisation is an effective method for restoring stability without the necessity of additional external fixation. Most likely the early rehabilitation reduced pulmonary complications, which in turn reduced early mortality of these fractures. The FEM could be used to identify the most appropriate implant configuration, since no well-established cadaver models exist.

Clinical Trial Registration: ClinicalTrials.gov, Identifier NCT02840695.

Keywords: ankylosing spondylitis, spinal fractures

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to my teachers
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


IV Robinson, Y., Olerud, C. Biological disease modifying anti-rheumatic treatment delayed spinal fractures in ankylosing spondylitis: National multi-registry cohort study from the Swedish patient registry and the Swedish prescribed drugs registry. *Submitted manuscript*

V Robinson, Y., Lison Almkvist, V., Olerud, C., Fahlstedt, M., Halldin, P. Finite element analysis of long posterior transpedicular instrumentation for cervicothoracic fractures related to ankylosing spondylitis. *Unsubmitted manuscript*

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### Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AS</td>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>ASAS</td>
<td>Assessment of SpondyloArthritis international Society</td>
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<tr>
<td>bDMARD</td>
<td>Biological disease modifying anti-rheumatic drugs</td>
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<td>CDR</td>
<td>Cause of Death Registry</td>
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<tr>
<td>CTJ</td>
<td>Cervicothoracic junction</td>
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<tr>
<td>DISH</td>
<td>Diffuse idiopathic spinal hyperostosis</td>
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<tr>
<td>EULAR</td>
<td>European League against Rheumatism</td>
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<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
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<tr>
<td>MTX</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>NPR</td>
<td>National patient registry</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<tr>
<td>PDR</td>
<td>Prescribed Drugs Registry</td>
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<tr>
<td>SIJ</td>
<td>Sacroiliac joint</td>
</tr>
<tr>
<td>SNHDR</td>
<td>Swedish National Hospital Discharge Registry (now NPR)</td>
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<tr>
<td>SpA</td>
<td>Spondylarthitis</td>
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<tr>
<td>SWESPIE</td>
<td>Swedish Spine Registry</td>
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Introduction

Pathogenesis and treatment of ankylosing spondylitis

Historical background

During the centuries several human skeletons with kyphotic deformities and fused vertebrae arose medical scientific attention, even though knowledge of the pathognomonic features of ankylosing spondylitis (AS) was unavailable (Figure 1). The first description of a skeleton with fused sacroiliac joints and complete spinal ankylosis is from 1691, when the Irish anatomist Robert Connor published his findings (Ebringer 2013). In 1748 Johann Sebastian Albrecht published a similar anatomical case report from Germany (Zorab 1961).

It was first the Russian Neurologist Vladimir Bechterew who was able to describe the pathology of ankylosing spondylitis (AS) in 1892, when he wrote that “based on the clinical data we may assume that we are dealing with a chronic process of the vertebrae that develops independently and leads to ankylosis. It also probably leads to a diffuse, chronic inflammation of the epidural connective tissue.” (Bechterew 1899).

The German Adolph Strümpell and French neurologist Pierre Marie added to the knowledge, thus the disease is even known as Morbus Bechterew-Strümpell-Marie.

Figure 1: Spinal skeleton with ankylosing spondylitis from the region of Heilbronn, early 6th century, shown at the Landesmuseum Württemberg, Stuttgart, Germany
Natural history of ankylosing spondylitis, classification and epidemiology

Ankylosing spondylitis (AS) is a rheumatoid disease leading to increased stiffness and eventually to a spontaneous fusion of all spinal segments from skull base to os ilium. Figure 1 depicts a typical skeleton of a patient with long history of AS. The disease commonly starts around the age of 25 with unspecific back pain and sacroiliac pain and is 3 to 4 times more common in men than in women (Dean, Jones et al. 2014). The disease itself belongs to the group of spondyloarthritides (SpA), where besides AS, psoriatic SpA, reactive SpA, SpA associated with inflammatory bowel disease and undifferentiated SpA are included (Braun and Sieper 2010). For axial SpA the Assessment of SpondyloArthritis international Society (ASAS) developed a classification based on specific SpA features and radiologically evident sacroiliitis or positive human leukocyte antigen (HLA)-B27 marker (Figure 2) (Rudwaleit, van der Heijde et al. 2009).

The prevalence of AS in 10,000 inhabitants is about 23.8 in Europe, 16.7 in Asia, 31.9 in North America, 10.2 in Latin America and 7.4 in Africa (Dean, Jones et al. 2014).

Table 1: Modified New York criteria (van der Linden, Valkenburg et al. 1984)

<table>
<thead>
<tr>
<th>1. Radiological criterion</th>
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<tr>
<td>Bilateral sacroiliitis grade ≥ II or unilateral sacroiliitis grade III to IV</td>
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<tr>
<th>2. Clinical criteria</th>
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<tr>
<td>(a) Low back pain and stiffness of at least 3 months duration improved by exercise and not relieved by rest</td>
</tr>
<tr>
<td>(b) Limitation of motion of the lumbar spine in both the sagittal and the frontal planes</td>
</tr>
<tr>
<td>(c) Limitation of chest expansion relative to values normal for age and sex</td>
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</tbody>
</table>

Definite AS is diagnosed if the radiological criterion plus 2 of the 3 clinical criteria are present.
Jones et al. 2014). The regional differences clearly suggest a genetic predisposition or an endemic infectious pathogenesis.

Pathogenesis

In patients with SpA typically signs of enthesitis, synovitis and osteitis are found (Taurog, Chhabra et al. 2016), enthesitis being the inflammation of the tendinous or ligamentous insertion. The trigger leading to the active expression of AS is still unknown. In rodents a T-cell mediated pathway involving IL-23 and IL17 leads to axial enthesitis (Sherlock, Joyce-Shaikh et al. 2012).

In 70-90% of all patients with axial SpA are HLA-B27 positive (Poddubnny and Sieper 2014). Up to 10% of those with HLA-B27 will develop SpA during their lives. This proportion is even higher if a relative has SpA (Taurog, Chhabra et al. 2016). The causality between HLA-B27 and AS is still unclear, but recent research suggests an involvement of the microbiome, where HLA-B27 plays a regulatory role (Kabeerdoss, Sandhya et al. 2016). This theory is supported by the finding that breastfeeding was protective against the development of AS (OR=0.53) (Montoya, Matta et al. 2016).

Figure 2: Classification criteria for axial spondyloarthritis (SpA) selected by the Assessment of SpondyloArthritis international Society (ASAS).

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Radiographical features and classification

AS has very typical radiographical features (Raychaudhuri and Deodhar 2014). Besides signs of sacroiliitis, the multilevel ankylosis of the whole spine is pathognomonic. The only radiographical differential diagnosis is the diffuse idiopathic skeletal hyperostosis (DISH), even called mb Forrestier, where several vertebrae are ankylosed by anterior spondylophytes (Olivieri, D’Angelo et al. 2009).

In order to identify patients in an early stage of AS plain radiographs are not sufficient, since it may take up to 10 years for the first structural lesions to appear on pelvic radiography. Magnetic resonance imaging (MRI) has the potential to detect inflammation at the very first manifestation of sacroiliitis (Weber, Østergaard et al. 2015). MRI found inflammation-related structural sacroiliac joint (SIJ) lesions in 60–90% of SpA patients already in the first 2 1/2 years after symptom debut (Weber, Jurik et al. 2016). The highest predictive value for axial SpA have SIJ bone marrow oedema together with erosions (Weber, Østergaard et al. 2015). Still the level of evidence is too low to allow diagnosis of axial SpA on MRI findings alone (Arnbak, Leboeuf-Yde et al. 2012).

In 1984 the modified New York criteria for AS diagnosis included besides radiographical signs of sacroiliitis, three clinical criteria of which two must be present to allow AS diagnosis (Table 1) (van der Linden, Valkenburg et al. 1984). The growing availability of HLA-B27 screening allowed to diagnose AS even in the absence of SIJ findings. Therefore, the currently most employed ASAS classification allows AS diagnosis based on HLA-B27 without presence of sacroiliitis, which reduced the significance of positive radiological signs (Figure 2). With the ASAS criteria approximately 95% of patients with AS could be predicted (Sepriano, Landewe et al. 2016).
Medical treatment

With diagnosis of AS comes the obligation to treat, in order to preserve quality of life and posture. Non-steroidal anti-inflammatory drugs (NSAID) have proven effect on function and disease progression and are therefore recommended as first line medication (Kroon, van der Burg et al. 2015). Sulfasalazine and Methotrexate have no effect on disease progression and are not recommended as standard medication (Chen, Veras et al. 2013, Chen, Lin et al. 2014). Biological disease modifying anti-rheumatic drugs (bDMARD) instead have proven effect on function and quality of life (Maxwell, Zochling et al. 2015).

Therefore, the current recommendations by the ASAS and the European League against Rheumatism (EULAR) for AS treatment are the following (Braun, van den Berg et al. 2011):

- NSAID are recommended as first-line drug treatment for AS patients with pain and stiffness.
- There is no evidence for the efficacy of glucocorticoids, sulfasalazine and methotrexate for the treatment of axial disease.
- bDMARD (anti-TNF) therapy should be given to patients with persistently high disease activity despite conventional treatments.
Physiotherapy

Physiotherapy is beneficial and an important complement to medical therapy (Dagfinrud, Kvien et al. 2005). Exercise for patients with ankylosing spondylitis should address the primary (musculoskeletal) consequences of AS, the secondary consequences of AS (cardio-respiratory, balance, osteoporosis), and facilitate physical activity with modification for AS symptoms, severity, activity and duration as required (Millner, Barron et al.). Interestingly, the effect of physiotherapy adds to the effect of bDMARD (Liang, Li et al. 2015).

Figure 3: Ankylosing spondylitis: progression of deformities. A photographic series of a patient with ankylosing spondylitis was taken over a period of 26 years. By 1957, a thoracic kyphosis has become apparent, and loss of the normal lumbar lordosis has occurred. There are early flexion contractures of the hips and knees. In the next 2 sequences, increasing flexion contractures of the hips and knees have occurred along with progressive ankylosis of the spine.

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Spinal complications of ankylosing spondylitis

Progressive kyphosis related to ankylosing spondylitis

AS typically leads to progressive global kyphosis with deteriorated sagittal profile (Figure 3). Due to the inflammation of the intervertebral joints, the disc loses its height prior to ankylosis, thus kyphosis occurs. Furthermore, isolated inflammatory lesions – Andersson lesions – are responsible for intermittent progress. These destructive disco-vertebral lesions were first described by Andersson in 1937 (Andersson 1937). They are caused by acute (aseptic) inflammation of the disc, but can even be caused by stress fractures (Bron, de Vries et al. 2009).

As soon as the kyphosis is established the unfavourable biomechanics with anterior column overload will induce further kyphosis progression until the whole spine is ankylosed (White, Panjabi et al. 1977).

Spinal fractures related to ankylosing spondylitis

Due to reduced biomechanical flexibility the spine in AS is experiencing long lever arms even when under minor trauma (Einsiedel, Schmelz et al. 2006), rendering it highly susceptible to instable vertebral fractures. The prevalent osteoporosis in AS adds to the risk of fractures (Carter and Lories 2011). A recent retrospective register study in more than 230,000 patients found a 3.3 times greater risk of vertebral fractures in patients with AS than in healthy patients (Vosse, Landewe et al. 2009). These fractures are associated with an increased mortality up to two years after fracture (Westerveld, Verlaan et al. 2009, Schoenfeld, Harris et al. 2011).

The case load of most regional spine centres is low for these fractures. Still there exists some published data in this regard, but only retrospective case series (evidence level 4). The systematic review of Westerveld et al (Westerveld, Verlaan et al. 2009) summarises the published results until 2008. Since then 6 new retrospective case series have been published on spinal fractures in AS (Table 2).

The published studies show clearly, that spinal fractures related to AS are highly associated with complications (Westerveld, Verlaan et al. 2009). Vertebral fractures cause an increased mortality in patients with AS with up to 50% mortality after 2 years (Whang, Goldberg et al. 2009, Schoenfeld, Harris et al. 2011). Common complications of surgery are up to 14% infection and up to 15% loosening (Backhaus, Citak et al. 2011).
Classifications of spinal fractures related to ankylosing spondylitis

Due to the biomechanics of the ankylosed spine the classical three- or two-column models are not applicable for spinal fractures related to AS or DISH (Heyde, Fakler et al. 2008). The new AOSpine fracture classification system therefore introduced the modifier M2 for ankylosing spine disease to mark the severity of the injury (Vaccaro, Oner et al. 2013). During the last decades, multiple specific classifications have been developed concerning spinal fractures related to AS.

In the Germanic region most commonly the classification by Metz-Stavenhagen et al (Metz-Stavenhagen, Krebs et al. 2001) is used, which describes two subtypes: Type I, the complete disruption of anterior and posterior bony and ligamentous structures, and type II, the sintering fracture, often after a minor injury, unnoticed by the patient, and the may easily be confused with an Andersson-lesion, the inflammatory discitis related to AS (Heyde, Fakler et al. 2008).

The classification of de Peretti et al (de Peretti, Sane et al. 2004) describes four fracture types according to their radiographic dislocation: Type I with anterior opening, type II with horizontal dislocation, type III non-displaced, and type IV being similar to spinal fractures unrelated to AS. The de Peretti type III fracture is related to delayed diagnosis, but no impact of fracture type on outcome was described (de Peretti, Sane et al. 2004). Furthermore, radiographic displacement classifications are highly sensitive to positioning of the patient during examination.

The classification introduced by Caron et al (Caron, Bransford et al. 2010) involves the radiographic course of the fracture line: Type I a transdiscal disruption, type II a vertebral body injury, and types III and IV being a combination of disc and vertebral body injuries. No impact of fracture type on patient treatment or outcome has been described until now. Since a transverse injury of the ankylosed spine can biomechanically be compared to a transverse diaphysary long bone fracture, the classification of “minor” radiographic differences remains academic and without any clinical impact.

Treatment of spinal fractures related to ankylosing spondylitis

Traditionally spinal fractures were treated non-surgically by external bracing, halo-vest or cast (Hunter & Dubo 1978, Pohl 1980, Graham and Van Peteghem 1989). Since non-surgical treatment was complicated and associated with high rates of non-union, the development of spinal instrumentation was embraced by surgeons treating patients with AS. Metz-Stavenhagen et al (Metz-Stavenhagen, Krebs et al. 2001) report non-union and revision in 20% and 17% mortality within 3 months for 25 patients treated surgically. Olerud
et al (Olerud, Frost et al. 1996) had a 100% fusion rate with surgical stabilisation and a 1-year-mortality of 29%.

Summarizing the published results of 345 patients with AS until 2009 Westerveld et al (Westerveld, Verlaan et al. 2009) found greater 3-month mortality in non-surgically treated patients with spinal fractures related to AS. Main cause of mortality was pneumonia or respiratory failure. Therefore, more and more surgeons prefer surgical treatment nowadays (Table 2).

One study stands out in this regard. Altun et al (Altun and Yuksel 2016) presented recently a series of 30 patients of which 18 were treated non-surgically. They found considerably more complications and no better fusion rate in surgically treated patients. Unfortunately, the authors did not address the significant selection bias, with more neurologically impaired patients in the surgical group. Therefore, their conclusion of non-surgical treatment as primary choice in elderly patients with AS and spinal fractures have to be read with caution.

**Anterior vs. posterior vs. circumferential surgical stabilisation**

Multiple surgical techniques have been developed to stabilise spinal fractures related to AS. Supporters of the anterior stabilisation technique for fractures related to AS point out that the anterior access is less traumatic, minimises the risks of displacement during positioning, and has less postoperative infections (Heyde, Fakler et al. 2008). And indeed, in non-ankylosed spinal columns most surgeons would choose an anterior approach to stabilise the non-compressed fracture, with the benefits of a lesser traumatic access, greater fusion rate, and kyphosis reduction (Dvorak, Fisher et al. 2007). But, even in the non-ankylosed spine the anterior-only approach is not recommended for transverse, rotationally unstable fractures (Dvorak, Fisher et al. 2007). Since spinal fractures related to AS are virtually almost transverse injuries there is no reason to deal differently with them. Beyond that, many patients with AS are highly kyphotic, and the anterior access is anatomically impossible. Furthermore, a long lever arm neutralisation of cervicothoracic fractures from anterior requires long anterior plates extending into the upper thoracic region, which then would require access extension into the upper mediastinum. Additionally, most surgeons do not routinely perform bi-cortical anterior screws, which would be necessary to get as much screw purchase as possible in the osteoporotic bone of the ankylosed spine. The inferiority of the anterior-only approach is reflected by the results of several studies, where implant failure solely occurred in the anterior-only treated patients (Zdichavsky, Blauth et al. 2005, Einsiedel, Schmelz et al. 2006).

Some authors regularly perform combined posterior-anterior or anterior-posterior stabilisation of patients with spinal fractures related to AS or DISH (Lu, Wang et al. 2009). This approach adds anterior stability to the posterior stabilisation (Heyde, Fakler et al. 2008). Unfortunately, the possible complications of the second access are added as well.
In our experience if a long posterior instrumentation is performed, the anterior access becomes will become obsolete, since stabilised fractures related to AS have a tendency to heal, even if anterior defects are present. In case of spinal cord compression by an irreducible anterior fragment, the anterior approach has to be added of course, but this is rarely found in the hyperextension injuries of patients with AS or DISH.

Table 2: Trials on spinal fracture treatment in ankylosing spondylitis published after 2008, that not included in the systematic review of Westerveld et al (Westerveld, Verlaan et al. 2009).

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Characteristics</th>
<th>Complications leading to revision surgery</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Backhaus et al 2011</td>
<td>Retrospective case series</td>
<td>N=129 (0 DISH) 51 cervical 55 thoracic 12 lumbar (51% SCI)</td>
<td>14% infection 15% loosening</td>
<td>32% mortality at 1 year</td>
</tr>
<tr>
<td>Caron et al 2010</td>
<td>Retrospective case series</td>
<td>N=112 (74 DISH, 28 AS) 67 cervical 39 thoracic 16 lumbar (52% SCI)</td>
<td>5% infection 10% loosening</td>
<td>32% mortality at 1 year</td>
</tr>
<tr>
<td>Sapkas et al 2009</td>
<td>Retrospective case series</td>
<td>N=20 (0 DISH) 7 cervical 12 thoracic 1 lumbar (50% SCI)</td>
<td>5% infection 10% loosening</td>
<td>32% mortality at 1 year</td>
</tr>
<tr>
<td>Whang et al 2009</td>
<td>Retrospective case series</td>
<td>N=12 10 cervical 2 thoracic 0 lumbar (67% SCI)</td>
<td>5% infection 10% loosening</td>
<td>32% mortality at 1 year</td>
</tr>
<tr>
<td>Altenbernd et al 2009</td>
<td>Retrospective case series</td>
<td>N=66 (70% SCI)</td>
<td>50% mortality after 2 years</td>
<td>32% mortality at 1 year</td>
</tr>
<tr>
<td>Altun et al 2016</td>
<td>Retrospective case series</td>
<td>N=30 18 cervical 11 thoracic 1 lumbar (37% SCI)</td>
<td>6.7% morbidity 3.3% mortality</td>
<td>3.3% mortality after 2 years</td>
</tr>
</tbody>
</table>
Aims

The aims of this thesis were

I. to identify the incidence of spinal fractures related to ankylosing spondylitis in Sweden
II. to describe the complications of the standard care for spinal fractures related to ankylosing spondylitis
III. to investigate whether surgical treatment improves survival after spinal fractures related to ankylosing spondylitis
IV. to demonstrate the effect of biological anti-rheumatic treatment on spinal fracture risk in patients with ankylosing spondylitis
V. to develop a finite element model that can be used to simulate spinal fractures related to ankylosing spondylitis and model their stabilisation
Patients and Methods

Study I – Incidence of spinal fractures related to ankylosing spondylitis

Sweden has a national public healthcare system, based on independent county councils, mainly financed by local taxes. The Swedish National Board of Health and Welfare registers data on hospital discharges in the Swedish National Patient Registry (NPR). Each record contains information about demographics, diagnoses, operations, and administrative data about the healthcare provider and the admission (Socialstyrelsen 2007, Ludvigsson, Andersson et al. 2011). Since 1987 more than 99% of all discharges are registered, and each year about 800,000 discharges are recorded (Table 1) (Socialstyrelsen 2007, Ludvigsson, Andersson et al. 2011). The validity of the data in the Register has previously shown to be adequate (Nilsson, Spetz et al. 1994, Ludvigsson, Andersson et al. 2011).

All patients with a primary discharge diagnosis of cervical, thoracic or lumbar vertebral fractures, spine dislocations, or disc ruptures were identified in the NPR (ICD-9: 805.0, 805.1, 805.2, 805.3, 805.4, 805.5; ICD-10: S12.0, S12.1, S12.2, S22.0, S22.1, S23.0, S23.1, S32.0, S32.1, S33.0, S33.1) (WHO 2006). Furthermore, all patients with the diagnosis of ankylosing spondylitis were identified (ICD-9: 720.0, ICD-10: M45). Spinal stabilisation surgery in these patients was identified by procedure codes (Swedish surgical procedure classification (until 1996): 8214, 8215, 8216, 8219, 8440, 8441, 8442, 8443, 8449, Swedish clinical procedure code (from 1997): NAJ, NAG, NAT)(Socialstyrelsen 2004).

Annual incidences of interest 1987 to 2009 were extracted by the Centre of Epidemiology of the Swedish National Board of Health and Welfare (www.socialstyrelsen.se), and population data was obtained by reports from the central bureau of Statistics Sweden (www.scb.se).

After adjusting of annual incidence for population growth, linear regression was applied for the annual incidence data and presented with variance $r^2$ and p-value.
Study II – Retrospective study on complications after posterior stabilisation of cervicothoracic spinal fractures related to ankylosing spondylitis

Patients with fractures of the cervicothoracic junction related to AS or DISH between 2007 and 2011 treated by posterior instrumentation at the first level trauma centre Uppsala university hospital, Sweden were eligible for inclusion. All patients were followed prospectively for two years using the standardised protocol of the Swedish Spine Registry (SWESPINE) (Zanoli, Nilsson et al. 2006). Recorded were patient-reported base-line data, complications, and pain, as well as surgeon-reported data on surgical method. Data on perioperative bleeding and surgical time were added after a journal review. Mortality data was obtained from the Swedish Cause of Death registry (CDR), where also survival data of all patients with subaxial cervical fractures (ICD-10: S12.2) treated between 1/1/1996 and 31/12/2011 registered in the Swedish National Patient Registry (NPR) were extracted.

The Statistical Package for Social Sciences (SPSS 22.0, IBM Corp., U.S.A.) was used to perform the statistical analysis. Mean values are presented with standard deviation, followed by intervals in brackets. The U-test by Mann, Whitney and White was applied to compare means. Mean survival was estimated with the Kaplan-Meier method. The impact of possible covariates on survival was analysed with a Cox regression model, and presented as hazard ratio (HR).
Study III – Survival of surgically and non-surgically treated patients with spinal fractures related to ankylosing spondylitis.

A dataset was extracted from the NPR containing anonymised patient numbers (allowing identification of duplicate registration), dates for admission, date of surgery, diagnosis codes (both ICD-9 and ICD-10), procedural codes for all patients with the diagnosis code of spinal fracture or AS from 1987 to 2011. Before anonymisation the dataset was cross-linked with the CDR and dates of death were added to the dataset allowing mortality investigations.

To identify spinal fractures ICD-9 diagnosis codes were used until 1996: 805A, 805B, 805C, 805D, 805E, 805F, 806A, 806B, 806C, 806D, 806E, 806F. Since 1997 the ICD-10 classification was used to identify spinal fractures: S12.0, S12.1, S12.2, S12.7, S12.8, S12.9, S13.0, S13.1, S13.2, S13.3, S22.0, S22.1, S23.0, S23.1, S32.0, S32.1, S33.0, S33.1. Hereafter all patients with ankylosing spondylitis were identified (ICD-9: 720, ICD-10: M45.9). To identify patients that underwent spine surgery procedure codes indicating stabilising spinal operations were used (Swedish surgical procedure classification (until 1996): 8214, 8215, 8216, 8219, 8440, 8441, 8442, 8443, 8449, Swedish clinical procedure code (from 1997): NAJ, NAG, NAT)(Socialstyrelsen 2004). Surgical treatment with decompression only was not considered as surgical stabilisation, and halo-treatment was considered as conservative treatment.

Duplicate entries were identified and only counted once, using the first time of admission with the diagnosis of a spinal fracture. If a patient was re-admitted with a spinal fracture >2 years after the previous admission, he was

Figure 4: Inclusion flow diagram for study III
counted and marked as a sequential fracture case and not removed as a duplicate. In the original dataset duplicate entries per patient reflect re-admissions possibly containing valuable diagnosis codes of co-morbidities. Therefore, all diagnosis codes for co-morbidities and later procedures on each patient were stored in a singular entry before erasing duplicate entries. This allowed for instance determining the Charlson Comorbidity Index (CCI) for each case (Charlson, Szatrowski et al. 1994). The inclusion flow diagram is presented in Figure 4.

The software R-studio version 0.99.489 (Free Software Foundation, Boston, MA, U.S.A) together with R commander (Version 3.3.0) (R_Core_Team 2016) was used to process the dataset and to perform the statistical analyses. A logistic regression model was used to determine the odds ratio (OR) of covariates on the treatment allocation. The Kaplan Meier method was employed to determine median survival and to plot the survival curve. Five Cox proportional hazards regression models were tested and the most predictive model applied to determine the hazard ratio (HR) of covariates (Bradburn, Clark et al. 2003). Results were presented with 95%-confidence intervals (95%-C.I.) and were considered as statistically significant if p<0.05.
Study IV – Biological disease modifying anti-rheumatic drugs delay spinal fractures related to ankylosing spondylitis.

Study Design
This national multi-registry cohort study uses prospectively collected electronic healthcare data from the Swedish National Patient Registry (NPR), the Swedish Cause of Death registry (CDR) and the Swedish Prescribed Drugs Registry (PDR) between 2005 and 2014. The study protocol was approved by the Institutional Ethical Review Board (no. 2015/147), registered with ClinicalTrials.gov (NCT02840695), and follows STROBE and RECORD statements. (von Elm, Altman et al., Benchimol, Smeeth et al. 2015)

Setting
The Swedish National Patient Registry is hosted by the Swedish National Board of Health and Welfare and contains all patient contacts within Sweden with a coverage of >90% for orthopaedic diagnoses. (Ludvigsson, Andersson et al. 2011) Registered are main diagnosis and co-morbidity using ICD-9 until December 1996, and since then the ICD-10 code. (WHO 2006) Treatment is coded since 1997 using the Swedish classification of surgical procedures. (Socialstyrelsen 2004) Furthermore, information on hospitalisation time is available from the registry.

Data collection for the Swedish Prescribed Drugs Registry (PDR) is administered by the National Corporation of Swedish Pharmacies, a governmental institution responsible for the provision of pharmaceutical services in the whole country. Since July 1st, 2005 information from all prescriptions dispensed is monthly transferred to the Centre for Epidemiology at the National Board of Health and Welfare, responsible for keeping the registry. (Wettermark, Hammar et al. 2007) The PDR uses Anatomical Therapeutic Chemical (ATC) codes for identification of medication group.

In the Swedish Cause of Death registry (CDR) all incident deaths and cause of death are registered for all patients. A validation of death certificates and registration document about 83% agreement for hospital deaths and 46% agreement for non-hospital deaths. (Johansson and Westerling 2000)

Participants
All patients registered with the main diagnosis of ankylosing spondylitis treated between January 1st, 1987 to December 31st, 2014 were extracted from the NPR. A second dataset was provided from the PDR including all prescriptions of anti-inflammatory drugs to patients in the dataset from the NPR between July 1st, 2005 to December 31st, 2014. Prior to data transmission, the Swedish National Board of Health and Welfare anonymised the individual personal identification numbers using a key which remained with the Agency. Since only patients with an active form of AS were of interest for this study,
patients younger than 40 and older than 70 years in 2014 were excluded. An inclusion flow diagram according to CONSORT statements illustrated the inclusion protocol. (Moher, Hopewell et al. 2010).

**Variables**

The ICD-9 code “720” and the ICD-10 code “M45.9” were used to identify patients with AS in the NPR. From the NPR baseline values as age, gender, date of hospitalisation was collected for each included individual. Additionally, co-morbidity was collected by storing co-incident ICD-9 and ICD-10 codes in each patient’s entry. Using ICD-codes the Charlson Comorbidity Index could be calculated for each patient using a previously validated algorithm. (Sundararajan, Henderson et al. 2004) Thereafter patients with spinal fractures 2011 to 2014 were identified in the NPR using ICD-10 codes S12.0, S12.1, S12.2, S12.7, S12.8, S12.9, S13.0, S13.1, S13.2, S13.3, S22.0, S22.1, S23.0, S23.1, S32.0, S32.1, S33.0, and S33.1.

To identify anti-inflammatory prescriptions, the PDR was searched for the ATC-codes for bDMARD (L04AA and L04AB), non-steroidal anti-inflammatory drugs (NSAID) (M01A), methotrexate (MTX) (L04AX), and sulfasalazine (A07EC01). Registered were number of prescriptions and years of treatment.

**Statistical methods**

The age distribution differences of AS patients with spinal fractures treated with and without bDMARD was visualised with a density distribution plot. A logistic regression analysis identified covariates of bDMARD treatment assignment and was presented with 95% confidence intervals (C.I.) and statistical probability p. (Bagley, White et al. 2001) Goodness-of-fit of the model was presented with pseudo-$r^2$ according to McFadden (McFadden 1973) and the p-value of the Hosmer-Lemeshow test. (Hosmer, Hosmer et al. 1997) To investigate the effect of years of bDMARD treatment on the spinal fracture debut a multivariate analysis of variance (MANOVA) was performed with years of MTX, sulfasalazine and NSAID treatment as covariates in the model and presented in APA style (American_Psychological_Association 2010). Fracture-free proportion by treatment with bDMARD was plotted using a Kaplan-Meier plot with 95% C.I. Proportional group differences were tested with the $\chi^2$-test.

As relevant covariates for the occurrence of a spinal fracture besides years of bDMARD treatment, years of NSAID treatment (Vosse, Landewe et al. 2009, Muñoz-Ortego, Vestergaard et al. 2014), and male gender (Caron, Bransford et al. 2010) were identified from systematic literature research.

All statistical calculations were programmed in R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria) (R_Core_Team 2016). Mean values were presented ± standard deviation if not indicated otherwise.
Groups were compared with t-test for normally distributed variables, otherwise the Wilcoxon-test was applied. Group proportions were tested with the χ²-test. A probability of p<0.05 was regarded as statistically significant.

Data access and cleaning methods

The authors did not have direct access to the national registry databases in this study, but were provided a predefined extract from the national registries by the Swedish National Board of Health and Welfare (specification no. 13062/2015).

Even though a clean patient registry dataset was provided, duplicates (recurrent admissions of the same patient or continued treatment in a secondary facility) had to be identified and removed from the extract. Prior to removal of duplicates, comorbidity data from duplicate records was stored in the unique patient record.

From the Prescribed Drugs Registry for each included patient the number of prescriptions 2005 to 2014 was extracted, as well as the number of years 2005 to 2014 when the patient received anti-rheumatic treatment.

Linkage

Individual patients in all three registries were identifiable by unique identification numbers. By searching the patient registry for diagnosis of AS a duplicate-free dataset of all included patients was created. The Cause of Death Registry was linked with this dataset using the MERGE function in R. For each patient in the dataset the number and years of prescriptions were identified after splitting the Prescribed Drugs Registry according to identification number, and then searching for prescriptions. Due to the unique identification number used in all three registries, the linkage quality which was controlled with 50 random samples was 100%.
Study V – Finite element analysis of long posterior transpedicular instrumentation for cervicothoracic fractures related to ankylosing spondylitis

**Soft- and hardware**

The adaptations of the model to the conditions of AS was performed on LS-PrePost version 3.2 on a Windows 7 system, while the running of the simulations were performed on a Linux machine running (CentOS 6.5), using LS-DYNA version R5.1.2.

**Connected FE-model**

In this study an existing validated model based on other connected models was used (Brolin and Halldin 2004). It includes the head, vertebrae, ligaments, muscles and intervertebral discs. This model will be referred to as the KTH-model.

The limbs and the trunk from the first thoracic vertebra and downwards was developed by Toyota to be used as a model in crash simulations. (THUMS, Total Human Model for Safety. AM50 Pedestrian Model: Version 1.4-060705. 2011. ©Toyota Motor Corporation, Toyota Central R&D Labs Inc.) This model will be referred to as the THUMS-model. Note that the head and neck of the original THUMS-model were replaced by the KTH-model. The THUMS-KTH model has been used by for example Alvarez et al. (2013) to test muscle activation in a pedestrian accident situation.

Figure 5 shows the full model that was used for the simulations in this study. It is shown with (a) and without (b) the parts representing muscles and soft tissue. Figure 2 shows a vertebra and the immediately superior intervertebral disc in the model. Colour coding was used simply to distinguish the different parts of the model.

**AS-spine adaptation**

The spine in late stage AS has following specific features:

1. all discs and all facet joints are fused (Cruickshank 1971),
2. osteoporosis of the vertebral bodies (Vosse and de Vlam 2009),
3. C0-C1 and C1-C2 are often still mobile (Slobodin, Shpigelman et al. 2015),
4. thorax and costovertebral ligaments provide passive stability (Sis, Mannen et al. 2016),
5. muscles provide active stability (Masi and Walsh 2003), and
6. kyphotic deformity of the cervicothoracic region (Liu, Qian et al. 2016).
In the model that was used as a foundation for this study, the discs were originally created with rings of shell elements inside solid elements. The solid elements represented the bulk material of the annulus fibrosus and the nucleus pulposus. The shell elements represented the fibrous structure of intervertebral discs.

In this study, AS was modelled by giving the outermost ring of shell elements bone tissue properties, while the inner rings were left unchanged. This simulated the disc in ankylosing spondylitis, where the annulus fibrosus is ossified and the central nucleous fibrosus is fibrotically remodelled but still highly mobile (Cruickshank 1971). In the case of the thoracic and lumbar spines, a new layer of shell elements had to be created at the outer edge of the discs.

These outermost shell elements were assigned a certain thickness and material properties to represent the extra bone tissue in the AS-spine, see Table 3: Disc AS ossification properties. The joints between the head and C1 as well as C1 and C2 are not connected with an intervertebral disc. These joints (C0-C1, C1-C2) were left untouched and not considered ossified.

In this version of the model the vertebrae were still considered rigid. Certain parts were given elastic properties in order to handle certain contact definitions but will be considered rigid when it comes to evaluating stresses and are not deformable. The disc ossifications were however given linearly elastic
properties. Figure 6 shows the intervertebral disc and its different parts: Nucleus pulposus, bulk material of annulus fibrosus, internal fibrous rings of annulus fibrosus and the outer ring (dark blue) that was used for the ossification in the case of AS.

**Fracture modelling**

The most common level for spinal fractures related to AS is at C6-C7 (Cornefjord, Alemany et al. 2005, Caron, Bransford et al. 2010, Robinson, Robinson et al. 2015). Therefore, a fracture model at C6-C7 was developed. This model requires that the fracture occurs through the ossified disc C6-C7 which was achieved by removing the shell elements representing the ossification at the chosen disc level. This meant that at the C6-C7 disc level there were no remaining elements of the ossification and the vertebrae (C6 and C7) were simply connected by the remaining elastic intervertebral disc elements. One has to assume that a spinal fracture related to AS may bear some load without severe dislocation, which may be true in axial compression loading. To simulate this the original disc nucleus was left intact at the fracture site, and only the elements representing the ossified annulus fibrosus were removed.

*Table 3: Disc AS ossification properties*

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young’s modulus</td>
<td>10GPa</td>
</tr>
<tr>
<td>Poisson’s ratio</td>
<td>0.2</td>
</tr>
<tr>
<td>Density</td>
<td>5.0g/cm³</td>
</tr>
<tr>
<td>Ossification thickness</td>
<td>1.0mm</td>
</tr>
</tbody>
</table>
**Instrumentation modelling**

The type of instrumentation that was chosen for this study was a system of posteriorly inserted screws connected with rods. In the model the individual screws and rods were simplified as circular cross-section beam elements. Because beam elements were used, threading of the screws, as well as any detailed screw-rod connection had to be omitted from this model.

Figure 7 shows the idea of connecting two sample vertebrae with the beam-implant.

Note the two screws for each vertebra.

In the model a screw consisted of a beam element that passed through the pedicle and the vertebral body. The anterior end of the beam was constrained to a node on the anterior surface of the vertebra. The beam was further constrained to a node on the posterior surface of the vertebra, at its exit point. Thus, each beam representing a screw was constrained to two points in the vertebra. The posterior end of the screw was then constrained to the rod. No rotations were allowed at the beams’ ends.

Figure 8 shows a lateral schematic view of the different instrumentation configurations that were chosen for investigation. The first variation, Figure 8a is denoted C6C7. It uses as few vertebral levels as possible, as well as the shortest possible rods. The next variation, Figure 8b, stabilises C3 to T3, which is the longest instrumentation that was investigated. This is denoted C3toT3. The variation in Figure 8c has a lesser screw density, while maintaining the

*Figure 7: Finite element model or two cervical vertebrae with short segment posterior pedicle screw implant, posterior view.*
same range of the fixation but skipping levels in between. This variation is denoted C3C6C7T3. The last variation, Figure 8d, is denoted C5toT1.

**Stability testing**

The chosen loading case for the model was inspired by a study by Siegmund et al. (Siegmund, Blouin Js Fau - Brault et al. 2007). There, healthy subjects where strapped onto a sled to which an acceleration was applied in the sagittal plane. The study aimed at measuring muscle activation. The applied acceleration was described as lasting from 0ms to 60ms with a peak of 1.55g at 16ms. This data was used to create load conditions for the model. In the model the acceleration was applied to the outer surface of the torso and arms, in the anterior direction. The torso was also constrained to allow movement only in the anterior-posterior direction. This was intended to constrain the model as if it was indeed strapped onto the sled used by Siegmund et al. (Siegmund, Blouin Js Fau - Brault et al. 2007). The intention was to create an extension-like movement of the head and cervical spine, since this is considered a common mechanism for injury in AS-patients (Einsiedel et al. 2006).

The simulations were performed with three different applied accelerations with three load factors: 1.5g, 3.0g and 4.5g. The shape of the load curve and time remained the same in the two new load cases as in the original. Figure 21 shows the basic shape of the load curve with a peak acceleration of 1.0g at 16ms. The end-time for the entire simulation was 300ms.

![Figure 8: Schematic lateral views of the different implant configurations. Dotted line indicates fractured disc level](image)
Simulations

Table 4 shows the seven model variations that were used. Each of the seven models was ran for the three different loads 1.5g, 3.0g, 4.5g resulting in a total of 21 simulations.

Output variables

To be able to study the impact of the different implant configurations, the following output variables were chosen.

*Rigid body rotations of the vertebrae*

Since the load is applied in the sagittal plane (anterior-posterior direction,) the rotation of the vertebrae in the sagittal plane was chosen to get an overview of the movements of each individual vertebra.

*Table 4: List of simulations*

<table>
<thead>
<tr>
<th>Model</th>
<th>Figure</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal model</td>
<td>-</td>
<td>The original model, representing a healthy patient with no AS.</td>
</tr>
<tr>
<td>AS, no fracture</td>
<td>-</td>
<td>Model with elements representing the ossification of parts of the intervertebral discs. This model represents the non-fractured AS-patient.</td>
</tr>
<tr>
<td>AS, fracture (at C6C7 disc level)</td>
<td>-</td>
<td>Model with removed elements in the disc ossification at the C6C7 disc level, representing a fracture.</td>
</tr>
<tr>
<td>AS, fracture, C6C7 implant</td>
<td>Figure 8(a)</td>
<td></td>
</tr>
<tr>
<td>AS, fracture, C3toT3 implant</td>
<td>Figure 8(b)</td>
<td></td>
</tr>
<tr>
<td>AS, fracture, C3C6C7T3 implant</td>
<td>Figure 8(c)</td>
<td></td>
</tr>
<tr>
<td>AS, fracture, C5toT1 implant</td>
<td>Figure 8(d)</td>
<td></td>
</tr>
</tbody>
</table>
Vertebral gap distance at fracture site
To get a measure of how well the instrumentation stabilized the fracture, the gap between two vertebrae at the fracture site was measured. More accurately, the gap distance in the results is defined as the deviation from the original distance between the vertebrae. Therefore, a vertebral gap distance that equals zero represents the original distance. The gap distance was calculated simply by measuring the distance between a node on the superior part and a node on the inferior part of the disc (Figure 9).

Both the gap distance in the anterior as well as the posterior part of the disc were calculated. However, the distance at the anterior part was chosen as the primary concern since it is furthest away from the instrumentation. (The original distance was measured to 5.63mm in the model.)

Translation of fracture
Translation in the horizontal plane of a vertebra in relation to a superior or inferior vertebra is always a risk factor since excessive translation may cause a vertebra to touch the spinal cord and cause neurological problems. Therefore, the horizontal movement of the vertebrae superior and inferior to the fractured disc was calculated. It shows, in effect, the shear distance of the C6 and C7 vertebra relative each other (Figure 10).

Stresses in the discs ossified parts
To get a measure of how the stresses vary depending on the different instrumentation configurations, the maximum principal stress in the ossified part of the discs were obtained for each disc ossification respectively.
Ethics

Registry based research implies handling of sensitive patient data. If the data is not anonymised a record in the registry could be connected to an individual, violating the individual privacy. Therefore, our data was anonymised by well-established standards of the Agency for Health and Welfare (socialstyrelsen) with minimal risk of data violation.

The individual’s autonomy is not violated if the researchers do not interact with the individual from the record. Therefore, informed consent is not deemed to be necessary. Since some of the studies in this thesis involve more than 17,000 individual patients, informed consent is practically impossible.

The aim of the registry-based research was to increase our knowledge on factors that affect our patients’ health and quality of life. It will therefore allow the development of more effective treatment strategies and even influence health policy.

The retrospective analysis of patient data for study II did not require any additional follow-up or radiographs, thus no patient harm was caused, except for the patient data violation by retrospective patient journal review.

Studies I to IV were approved by the Regional Research Ethics Board of Uppsala (dnr 2010/297, dnr 2010/131/1, dnr 2010/297/1, and dnr 2015/147). Study V does not involve patients or sensitive data which would require ethical approval.
Results and discussion

Study I

Results

During the years 1987 to 2008 a total number of 17764 patients with AS were registered as inpatients. The annual hospitalisation incidence until 2000 showed a relatively stable interval between 624 and 823 patients, but from 2001 onward a linear increase from 650 in 2001 to 1226 in 2008 was seen (r=0.99, p<0.001). The population in Sweden grew between 1987 and 2008 at an average rate of 0.46% every year.

![Graph showing incidence of spinal fractures in AS and incidence of operated cases](image)

*Figure 11. Incidence of spinal fractures in AS (red line) and incidence of operated cases (blue line).*

About 4.1% (n=724) of patients with AS had fractures of the spine. There was a positive linear trend in the annual incidence of AS-patients with spinal fractures (r=0.94, p<0.001) (Figure 11). The proportion of spine fractures in admitted AS patients increased starting from 0.82% in 1987 up to 11.3% in 2008.

During the recorded time period 369 of these were operated on with spinal stabilisation surgery. The total number of operated patients with AS and spinal fractures increased linearly over the years (r=0.93, p<0.001) (Figure 11).
Even the relative proportion of patients with vertebral fractures receiving surgical therapy increased by 2.9% annually ($r=0.89$, $p<0.001$) (Figure 12). In 1987 only one patient was operated on, while in 2008 56 patients received operative stabilisation.

**Figure 12.** Proportion of surgically treated patients with spinal fractures related to ankylosing spondylitis.

**Discussion**

During the last two decades a steady increase in the incidence of spinal fractures in patients with AS was found in Sweden. Although it has been suggested that through better medical treatment of AS the risk of suffering an unstable fracture should be reduced, this has not been found in this analysis of this register data. The data from the NPR does not allow similar conclusions as a recently published study in 758 patients with AS by Vosse et al. (Vosse and de Vlam 2009) presenting reduced fracture risk if the patients were receiving medical therapy (OR 0.65). Swedish healthcare resource utilisation in patients with AS did not differ from other developed countries with 6-7 physician visits annually, thus improved medical therapy according to international guidelines should be expected during the last decades (Strombeck, Englund et al. 2010). Thus either the effect of medical therapy has not reached epidemiological significance, yet, or other underlying factors have to be put into consideration.
The observed increase in total numbers of vertebral fractures in all regions of the spine is accompanied by a relative decline in cervical and lumbar fractures in favour of thoracic fractures. In the last years there has been a positive trend towards the use of computed tomography instead of conventional radiographs especially in patients with AS (Harrop, Sharan et al. 2005). A decreased number of missed fractures could explain the relative increase in thoracic fractures, which can be hard to visualise on plain radiographs. Other possible explanations as a change in trauma patterns, and reduced ankylosis of cervical and lumbar spine are only hypothetical and lack any supporting evidence.

As the fracture rate in patients with AS increases, the number of patients receiving surgical therapy increased annually. This trend is in line with the growing understanding of biomechanics of the ankylosed spine, requiring rigid fixation of long lever arms. Due to the biomechanical superiority and facilitation of patient mobilisation, instrumented surgery is now the treatment of choice (May, Raunest et al. 2002), leaving conservative treatment for the minority of cases where surgical therapy is not an option due to co-morbidity, and cases where halo-vest-treatment can be applied successfully (Heyde, Fakler et al. 2008).

Regardless of the underlying causes, an obvious increase in the number of vertebral fractures in patients with AS could be observed. It seems that the improved quality of life and function in these patients (McLeod, Bagust et al. 2007) does not correlate with a reduced fracture risk. Thus all medical practitioners are urged to inform all patients with AS to keep a high safety profile when engaging in sports or other activities that could lead to injuries due to the increased fracture risk.

Study II

Results

Between 2007 and 2011 41 patients (35 men, 6 women, age 71±12 years [48-95]) with fractures of the cervicothoracic junction (CTJ) related to AS or DISH were treated by posterior instrumentation. Of the 41 patients included in this study 31 had fractures of the CTJ related to AS, 10 patients had DISH. All fractures were involving anterior and posterior, bony and ligamentous structures of the spine at the level of injury, and were classified as type I according to Metz-Stavenhagen et al (Metz-Stavenhagen, Krebs et al. 2001). All fractures were hyperextension injuries and classified type B4 M2 according to the new AOSpine classification (Vaccaro, Oner et al. 2013). One patient had a C2-C3 injury, one patient a C3-C4 injury, 5 patients a C4-C5 injury, 5 patients a C5-C6 injury, 20 patients a C6-C7 injury and 9 patients a C7-T1 injury.
Neurologic deficit was found in 11 patients (6 Frankel A, 4 Frankel C, 1 Frankel D). The remaining patients had no neurological deficit (30 Frankel E).

All patients were treated by posterior stabilisation from the upper cervical to the upper thoracic spine using titanium screw-rod systems. Screws were inserted in three vertebrae cranially and three vertebrae caudally of the injury. If extending to C1, Goel-Harms screws were placed, in C2 short, non-transarticular Magerl-screws, subaxially in most cases lateral mass screws, while in the thoracic spine transpedicular screws were inserted three levels below the injury. 37 of the instrumentations were cranially extending to C2, 2 to C1 and 2 to occiput. Caudally in 44% the instrumentation ended at Th3, in 27% at Th2. Decompression by laminectomy was performed in the 11 cases with neurological deficit. Mean surgical time starting from the placement of the skull clamp to the release of the skull clamp was 255±90min [80-488], bleeding 2128±3005ml [300-17000]. Postoperatively no external immobilisation was applied.

Pre-existing co-morbidity was common. Six patients were smokers. Arterial hypertension was found in 24 patients, and a cardiac co-morbidity was present in 16 patients. Diabetes mellitus was evident in 9, of which 5 were insulin dependent. 7 Patients had some kind of psychiatric disorder. Four patients had pulmonary and 4 had renal co-morbidity. Three patients had a history of malignancy.

Five patients suffered from postoperative infections, of which 4 could be treated with antibiotics alone, but one required revision surgery. Three patients had postoperative pneumonia, 2 patients required postoperative tracheostomy due to pulmonary insufficiency, and 1 patient had postoperative cerebrospinal fluid (CSF) leakage due to accidental durotomy.

At one-year follow-up the patients reported a neck-pain of 24±25 [0-85] and an arm-pain of 21±24 [0-84] on the 100 points VAS scale. Neck pain improved after 2 years to 14±18 [2-54] VAS, arm pain to 20±27 [0-67]. No patient required re-operation due to implant failure or non-union during the first two years.

The mean survival was 52±5 months (95% CI: 42-62). The Kaplan-Meier survival plot is presented in Figure 13. Cox regression analysis revealed that survival was significantly affected by patient age (HR=1.22; p<0.001), female gender (HR=0.05; p=0.024), smoking (HR=23.23; p=0.038), and Frankel A spinal cord injury (HR=8.31; p=0.020). Survival was not affected by the type of ankylosing disease, co-morbidities, level of cranial or caudal fixation, surgical time, or amount of surgical bleeding.
Discussion

Complications of posterior spinal fracture stabilisation in ankylosing spine disease

Patients with ankylosing spine disease suffering from a fracture of the cervical spine or the cervicothoracic junction are high-risk patients. 1. The fracture itself is due to the long lever arms of the cranial and caudal fragment highly unstable and requires rigid stabilisation measures, involving neutralisation of lever arms (Heyde, Fakler et al. 2008). 2. The transverse injury of all bony (and ligamentous) structures endangers the spinal cord, and neurology may deteriorate, if complete SCI is not already present after the injury (Heyde, Fakler et al. 2008, Caron, Bransford et al. 2010). 3. Due to the patients’ usually kyphotic deformity, which is often prevalent after lifelong AS, external stabilisation is troublesome, since collars will not fit and halo-type fixations will loosen if the head is positioned more anteriorly. 4. The osteoporosis related to AS may cause delayed union due to implant loosening, and subsequently instrumentation failure (Carter and Lories 2011). 5. The reduced soft tissue coverage over the cervicothoracic junction in ankylosed patients predisposes for

![Survival functions of surgically treated patients with cervical fractures](image.png)

*Figure 13: Kaplan-Meier plots of the observed survival of surgically treated cervical fractures in this study (only AS and DISH, n=41) and surgically treated cervical fractures in the Swedish National Patient Registry between 1996 and 2011 (n=2059).*
wound healing deficiency, especially in the presence of kyphosis. 6. Thoracic rigidity related AS reduces pulmonary function thus facilitating complications involving the respiratory system (Ragnarsdottir, Geirsson et al. 2008). 7. Considerable surgical blood loss related to AS must be expected, which may require massive transfusion (Tetzlaff, Yoon et al. 1998). 8. Most patients with fractures related to ankylosing spine disease are at a higher age, and often have numerous co-morbidities (Caron, Bransford et al. 2010). Complications are therefore expected, and in most cases rather related to the underlying disease than to the surgical treatment.

The retrospective study by Caron et al (Caron, Bransford et al. 2010) reported complications in 84% of the 112 patients treated for fractures in ankylosing spine disease, most of them similar to those found in our study group Table 5. They had pulmonary complications in 35% of all treated patients, but could not relate this complication to the type of treatment. Whang et al (Whang, Goldberg et al. 2009) found pulmonary complications in 13% of the 30 treated cases. Interestingly, all three reported fatal pulmonary complications occurred in patients with halo vest treatment, again demonstrating the drawback of external cervical immobilisation (Majercik, Tashjian et al. 2005).

In the series of de Peretti et al (de Peretti, Sane et al. 2004) 63% of the 48 conservatively treated patients with AS or DISH had bed-rest-related complications, as decubital ulcers or pneumonia. With regard to the in this context relatively low rate of pulmonary complications in the present study, a positive impact of early rehabilitation without the necessity of bed rest, orthosis or halo vest immobilisation can be assumed, which will influence both complication rate and mortality.

Spinal fractures related to AS or DISH are associated with considerable bleeding (Tetzlaff, Yoon et al. 1998). It is generally known that patients with AS have a greater amount of blood loss. Reasons for this may be 1. complicated positioning causing vena cava compression, 2. increased vascularity if skeletal structures due to the inflammatory neo-vascularisation, and 3. unawareness and delay of massive transfusion protocol activation (Tetzlaff, Yoon et al. 1998). Olerud et al (Olerud, Frost et al. 1996) had a mean surgical blood loss of 3500ml [0-16500ml], Cornefjord et al (Cornefjord, Alemany et al. 2005) 2119ml [450–6800ml], Lu et al (Lu, Wang et al. 2009) 2100ml, and our study 2128ml [300-17000ml]. Multiple cases with massive blood loss are described. Olerud et al (Olerud, Frost et al. 1996) had two cases of bleeding >10 liters, Tetzlaff et al (Tetzlaff, Yoon et al. 1998) one case with 17 liters blood loss, and our study had one case of 17 litres massive blood loss. Early communication of the expected blood loss, and timely activation of the massive transfusion protocol is recommended to avoid deterioration of this potentially fatal condition (Baumann Kreuziger, Morton et al. 2014).
Table 5: Published complications related to treatment of ankylosing spine diseases. Most studies were including even thoracic and lumbar fractures.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Study II</th>
<th>Caron et al.</th>
<th>Lu et al.</th>
<th>Whang et al.</th>
<th>Einsiedel et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>2014</td>
<td>2010</td>
<td>2009</td>
<td>2009</td>
<td>2006</td>
</tr>
<tr>
<td>N (all)</td>
<td>41</td>
<td>112</td>
<td>18</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td>N (surgical)</td>
<td>41</td>
<td>75</td>
<td>18</td>
<td>22</td>
<td>37</td>
</tr>
<tr>
<td>Wound infection</td>
<td>12%</td>
<td>16%</td>
<td></td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>7%</td>
<td>35%</td>
<td>11%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>5%</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dural tear</td>
<td>2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidural hematoma</td>
<td>0%</td>
<td>7%</td>
<td></td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>0%</td>
<td>8%</td>
<td></td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Loss of fixation</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>7%</td>
<td>14%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Publication</th>
<th>Zdichavsky et al</th>
<th>Cornefjord et al</th>
<th>De Peretti et al</th>
<th>Hitchon et al</th>
<th>Olerud et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (all)</td>
<td>32</td>
<td>19</td>
<td>48</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>N (surgical)</td>
<td>30</td>
<td>19</td>
<td>0</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>Wound infection</td>
<td>9%</td>
<td>0%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>16%</td>
<td>26%</td>
<td>63%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheostomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dural tear</td>
<td></td>
<td></td>
<td></td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Epidural hematoma</td>
<td></td>
<td></td>
<td>6%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of fixation</td>
<td>10%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>23%</td>
</tr>
</tbody>
</table>
With regard to loss of fixation the available publications present a dramatic reduction of implant or fixation failures during the last decades (Table 5). While Olerud et al (Olerud, Frost et al. 1996) reported 1996 a loss of fixation in 23% of the treated cases, Einsiedel et al (Einsiedel, Schmelz et al. 2006) found 2006 only 14% failures, which was further improved 2009 in the study by Whang et al (Whang, Goldberg et al. 2009) to 7% and in 2010 by Caron et al (Caron, Bransford et al. 2010) to 1%. The case series of thoracolumbar fractures related to AS by Hitchon et al (Hitchon, From et al. 2002) of 2002 sticks out in this regard, since it was free of implant failures. They chose in contrast to most published studies of that time continuously a multilevel posterior approach for surgical fracture stabilisation. This approach has been popularised during the last decade and recently published studies have few cases of implant failure. In the presented study the multilevel posterior-only approach was chosen, which had successful results with regard to healing and implant stability. Obviously the long posterior lever arm neutralisation was biomechanically reasonable.

One major drawback of posterior stabilisation in the CTJ is the critical soft tissue covering of the mostly severely kyphotic area. Postoperative wound infections of up to 16% were reported, requiring in some cases revision surgery and/or long-term antibiotic treatment (Caron, Bransford et al. 2010). In our series 12% of the treated patients sustained postoperative infections, most of which could be treated non-operatively. A major problem in patients with AS is the inactivity-related reduced muscle covering over the CTJ. Inappropriate re-insertion of interscapular and trapezius muscle may facilitate wound dehiscence and infection. This is supported by the finding that surgical invasiveness was associated with postoperative wound infections (Cizik, Lee et al. 2012). Furthermore, prominent spinous processes may be a constant threat to CTJ skin covering, and may need revision surgery with resection of these bony structures (Olerud, Frost et al. 1996).

Table 6: Published 1-year mortality after spinal fracture treatment in ankylosing spine diseases.

<table>
<thead>
<tr>
<th>Publication</th>
<th>1-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study</td>
<td>24%</td>
</tr>
<tr>
<td>Schoenfeld et al (Schoenfeld, Harris et al. 2011)</td>
<td>33%</td>
</tr>
<tr>
<td>Caron et al (Caron, Bransford et al. 2010)</td>
<td>32%</td>
</tr>
<tr>
<td>Meyer et al (Meyer 1999)</td>
<td>31%</td>
</tr>
<tr>
<td>Olerud et al (Olerud, Frost et al. 1996)</td>
<td>26%</td>
</tr>
<tr>
<td>Rowed et al (Rowed 1992)</td>
<td>29%</td>
</tr>
</tbody>
</table>
Spinal cord injury and mortality of cervical fractures related to AS or DISH

In our series 27% had spinal cord injury associated with the injury. Caron et al (Caron, Bransford et al. 2010) had 58%, and Whang et al (Whang, Goldberg et al. 2009) even had 67% with spinal cord injury. The high occurrence of SCI documents well the neurological hazard a fracture related to ankylosing spine disease represents. Caron et al (Caron, Bransford et al. 2010) found during follow-up improved neurological function in 34% of the patients, still 5% had worsened neurology. Rowed et al (Rowed 1992) even reported 19% with worsened neurology following initial treatment. Common reasons for neurological deterioration are dislocation of the fracture with spinal cord compression and epidural hematoma. Already during the prehospital resuscitation and transport, neurologically fatal fracture dislocations may occur, if a patient with a kyphotic deformity is forced onto a spine board. Tracheal intubation often requires fiberoptic assistance to avoid dislocation of a cervical fracture. Furthermore, fracture displacement may occur in the operating theatre during patient positioning in general anaesthesia, where neither muscle tone nor reported pain protect the spinal cord from injury (Fox, Onofrio et al. 1993, Sciubba, Nelson et al. 2008). Dislocation with neurological worsening may even occur during conservative fracture treatment (Aoki, Yamagata et al. 2013). Extensive bleeding from ruptured epidural veins and the cancellous bone of the vertebral fracture may cause severe epidural hematoma (Jacobs and Fehlings 2008). Fracture mobility hinders proper clotting, and an initially harmless fracture hematoma can develop into a large epidural mass causing spinal cord compression. This is especially true if the patient has clotting malfunction.

It is well known that spinal cord injury is associated with greater mortality (Lidal, Snekkevik et al. 2007). With regard to the considerable number of patients with spinal cord injury the relatively high mortality of spinal fractures related to ankylosing spondylitis is not surprising. The published 1-year mortality after fractures related to ankylosing spine disease ranges between 24% and 33% (Table 2). A patient in Sweden with a surgically treated subaxial cervical fracture without AS has a mean survival of 218 months (95% CI: 213-225; unpublished data from 2059 cases in the Swedish National Hospital Discharge Registry), but the patients in our study only had a mean survival of 52 months (95% CI: 42-62) (Figure 2). Other factors than ankylosing spine disease may have an influence on patient survival and are not adjusted for in this comparison. E.g. the patients have higher age and more co-morbidity in our study than in the general e-spine trauma population. In our study population, survival was significantly affected by complete spinal cord injury (Frankel A) associated to the fracture. The series in patient with DISH-related cervical fractures by Meyer et al (Meyer 1999) found a strong association of neurological injury and mortality, as well, while, despite the relatively high number of
included patients, Caron et al (Caron, Bransford et al. 2010) could not relate spinal cord injury to increased mortality. Still, most studies agree, that about 25% of patients with spinal fractures related to AS or DISH do not survive longer than one year after the injury.

Fractures of the cervicothoracic junction related to ankylosing spondylitis or DISH are highly unstable injuries, and most patients suffer from multiple complications during treatment. The suggested type of treatment using long posterior constructs allows early rehabilitation without bracing at a considerably low complication rate. In most patients the posterior instrumentation construct is biomechanically most feasible and rarely requires additional anterior support (Cornefjord, Alemany et al. 2005). Long posterior constructs in case of cervical fractures related to AS or DISH should be considered as primary choice, while other stabilisation measures may have their place, but seem to be inferior with regard to biomechanical stability.

Study III

Results

A total of 32088 hospital admissions with ankylosing spondylitis were registered in the NPR between 1987 and 2011 (Figure 4). After removal of duplicate entries 17297 cases remained. The inclusion flow chart is presented in Figure 4. During the included 990 hospital admissions 1131 AS-related spinal fractures were treated. Sequential fractures with separate admissions of an individual patient were found in 61 cases. Baseline data according to treatment allocation is presented in Table 7.

Male patients and patients with spinal cord injury were more likely to be operated on, as well as patients operated during the more recent years. Table 8 presents the OR of covariates in the logistic regression model.

The proportion of surgically treated spinal fractures increased linearly during the last decades ($r=0.92, p<0.001$) and has been about 64% throughout the observed time period (Figure 12).
Table 7: Baseline values of included cases with spinal fractures related to ankylosing spondylitis

<table>
<thead>
<tr>
<th></th>
<th>Surgical</th>
<th>Non-surgical</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>636</td>
<td>354</td>
<td>990</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± sd</td>
<td>65.4 ± 12.7</td>
<td>66.2 ± 15.0</td>
<td>65.7 ± 13.6</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n male</td>
<td>547</td>
<td>273</td>
<td>820</td>
</tr>
<tr>
<td>n female</td>
<td>89</td>
<td>81</td>
<td>170</td>
</tr>
<tr>
<td><strong>CCI mean ± sd</strong></td>
<td>4.8 ± 2.4</td>
<td>4.7 ± 2.5</td>
<td>4.8 ± 2.4</td>
</tr>
<tr>
<td><strong>cervical fracture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>381</td>
<td>153</td>
<td>534</td>
</tr>
<tr>
<td><strong>thoracic fracture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>238</td>
<td>114</td>
<td>352</td>
</tr>
<tr>
<td><strong>lumbar fracture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>115</td>
<td>130</td>
<td>245</td>
</tr>
<tr>
<td><strong>multilevel fracture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>91</td>
<td>39</td>
<td>130</td>
</tr>
<tr>
<td><strong>sequential fracture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>40</td>
<td>21</td>
<td>61</td>
</tr>
<tr>
<td><strong>Spinal cord injury</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>122</td>
<td>41</td>
<td>163</td>
</tr>
</tbody>
</table>

Table 8: Odds Ratio (OR) and 95% C.I. of covariates for surgical treatment allocation.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>OR</th>
<th>95% C.I.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.98</td>
<td>1.01</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.52</td>
<td>1.05</td>
<td>2.19</td>
</tr>
<tr>
<td>Cervical fracture</td>
<td>1.00</td>
<td>0.27</td>
<td>4.18</td>
</tr>
<tr>
<td>Thoracic fracture</td>
<td>0.71</td>
<td>0.19</td>
<td>3.01</td>
</tr>
<tr>
<td>Lumbar fracture</td>
<td>0.35</td>
<td>0.09</td>
<td>1.46</td>
</tr>
<tr>
<td>Multilevel fractures</td>
<td>2.36</td>
<td>0.47</td>
<td>10.82</td>
</tr>
<tr>
<td>Sequential admissions</td>
<td>0.75</td>
<td>0.42</td>
<td>1.38</td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td>2.73</td>
<td>1.77</td>
<td>4.31</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>0.99</td>
<td>0.91</td>
<td>1.08</td>
</tr>
<tr>
<td>Year of admission</td>
<td>1.11</td>
<td>1.08</td>
<td>1.14</td>
</tr>
</tbody>
</table>
Of the 17297 cases from the NPR with AS 4897 had already deceased according to the CDR. In the included 990 cases of AS patients with spinal fractures the median survival was 8.9 years (95% C.I.:7.75-10.0); the 3-month mortality was 17%. The most predictive Cox regression model found age, gender, SCI and CCI contributing to mortality in this cohort ($r^2=0.339$). Surgical stabilisation had a positive impact on survival (HR=0.79, p=0.027). Survival of AS-related spinal fractures was improved by being hospitalised now and not years ago (HR=0.96, p<0.001). Results for covariates in the Cox proportional hazards model are presented in Table 9.
Figure 14: Linear trend in annual proportion treated surgically for spinal fractures related to ankylosing spondylitis ($r=0.90$, $p<0.001$).

Table 9: Hazard Ratio (HR) and 95% C.I. of covariates for mortality in the Cox proportional hazards model.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>HR</th>
<th>95% C.I. lower</th>
<th>95% C.I. upper</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05</td>
<td>1.04</td>
<td>1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.29</td>
<td>1.00</td>
<td>1.66</td>
<td>0.049</td>
</tr>
<tr>
<td>Cervical fracture</td>
<td>1.66</td>
<td>0.63</td>
<td>4.39</td>
<td>0.309</td>
</tr>
<tr>
<td>Thoracic fracture</td>
<td>1.32</td>
<td>0.49</td>
<td>3.53</td>
<td>0.579</td>
</tr>
<tr>
<td>Lumbar fracture</td>
<td>1.33</td>
<td>0.50</td>
<td>3.50</td>
<td>0.567</td>
</tr>
<tr>
<td>Multilevel fractures</td>
<td>0.69</td>
<td>0.23</td>
<td>2.06</td>
<td>0.505</td>
</tr>
<tr>
<td>Sequential fractures</td>
<td>0.94</td>
<td>0.59</td>
<td>1.50</td>
<td>0.806</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>0.79</td>
<td>0.64</td>
<td>0.98</td>
<td>0.029</td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td>1.55</td>
<td>1.22</td>
<td>1.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>1.28</td>
<td>1.22</td>
<td>1.35</td>
<td>0.000</td>
</tr>
<tr>
<td>Year of admission</td>
<td>0.96</td>
<td>0.95</td>
<td>0.98</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Discussion

The main findings of this study were (1) an improved survival with surgical stabilisation of patients with spinal fractures related to ankylosing spondylitis, (2) a dramatic impact of spinal cord injury on the overall mortality of these patients, (3) a significant trend towards surgical management of spinal fractures related to AS, and (4) an improved survival of patients with spinal fractures related to AS during the last decades.

**Improved survival by surgical stabilisation**

In this study surgical stabilisation had a clear beneficial effect on survival of spinal fractures related to AS. Until now, little is published on the effect of surgery on survival. The meta-analysis of publications between 1980 and 2007 by Westerveld et al. (Westerveld, Verlaan et al. 2009) finds no significant effect of surgery on survival. In 2010 Caron et al. (Caron, Bransford et al. 2010) review retrospectively 112 patients with spinal fractures related to AS or DISH. They find a 1-year mortality of surgically treated patients of 23% (17 of 75), compared to 51% (19 of 37) with non-surgical treatment ($\chi^2$-test, $p=0.005$). In this context the results from our study seem valid.

For the treatment allocation in the presented dataset a significant selection bias must be assumed. Both, patients with simple non-displaced fractures, and those with considerable comorbidity are likely to receive non-surgical treatment (Westerveld, Verlaan et al. 2009), while those with fracture dislocation, SCI, and relatively good health are more likely to be operated on. The descriptive statistics of the present dataset revealed that those with SCI were more likely to be treated surgically, but those with lumbar fractures were in the majority of cases treated non-surgically. Patient comorbidity as measured with the CCI did not play a major role in treatment decision. Considering the above mentioned confounders fracture location and SCI entered as independent covariates the Cox-regression analysis, and still surgical treatment remained to be a significant predictor for survival. As fracture displacement was not accessible in our database, this factor could not be adjusted for. Assuming that a fracture would be treated rather surgically the more it is displaced, adding fracture displacement could only strengthen the beneficial effect of surgical treatment.

With regard to the surgical treatment of spinal fractures related to AS, multiple complications are common. Wound infections of up to 16%, pulmonary complications of up to 63%, and mechanical complications of up to 23% are described (Olerud, Frost et al. 1996, de Peretti, Sane et al. 2004, Caron, Bransford et al. 2010, Chikuda, Yasunaga et al. 2013, Robinson, Robinson et al. 2015). Some of these complications may be associated with mortality by themselves (Robinson, Robinson et al. 2015). However, the risk of surgical complications did not attenuate the positive effect on survival found in the SPR.
Predictors of mortality

In our study the 3-months-mortality of patients with spinal fractures related to AS was 17%, which has intriguing similarity to the 3-months mortality of 18% that Westerveld et al. (Westerveld, Verlaan et al. 2009) report.

As in most previously investigated populations, age and sex were associated with mortality. Furthermore, patient comorbidity played a major role for surgical survival. This study confirmed that the Charlson Comorbidity Index is associated with postoperative mortality (Chikuda, Yasunaga et al. 2013).

Spinal cord injury was related to considerable mortality in patients with ankylosing spondylitis. It is well documented that spinal cord injury in AS patients is associated with mortality, being greater the more cranial and the more complete the lesion is (Alaranta, Luoto et al. 2002, Wilson, Cadotte et al. 2012). A recently published cohort study finds survival of surgically treated cervicothoracic injuries in AS to be threatened by complete spinal cord injury (HR=8.3, p=0.02) (Robinson, Robinson et al. 2015). The avoidance of spinal cord injury by preventive measures and proper prehospital stabilisation, and the awareness of the particular circumstances required for SCI rehabilitation will reduce the mortality of spinal injuries related to AS (W. Bradley Jacobs and Michael G. Fehlings 2008).

Current treatment trend towards surgery and improved survival

For decades many have avoided surgical treatment of spinal fractures related to AS, since the injured patients often were in a poor condition complicated by co-morbidity (Graham and Van Peteghem 1989). Thus non-surgical treatment has been applied in many patients. External immobilisation of spinal fractures related to AS requires well-experienced staff, and time-consuming nursing (Graham and Van Peteghem 1989). Unfortunately, even under the most optimal conditions complications are common, and the mortality is high (Caron, Bransford et al. 2010, Chaudhary, Hullinger et al. 2011).

During the last two decades there was a trend in Sweden towards surgical treatment of these fractures being today around 70%. This reflects the growing number of recommendations to treat spinal fractures related to AS surgically (Heyde, Fakler et al. 2008, Westerveld, Verlaan et al. 2009, Caron, Bransford et al. 2010). The treatment rationale behind these recommendations is based on the biomechanical understanding, that fractures of the ankylosed spine liken transverse diaphysary long bone fractures. Long lever arms cranially and caudally of the fracture interfere with bony healing, and non-union will result if sufficient stability is not provided. Therefore, a long posterior fixation of at least 3 level above and below the fracture is recommended by several authors (Caron, Bransford et al. 2010, Backhaus, Citak et al. 2011).

Following these recommendations, the survival of spinal fractures related to AS improved in Sweden during the last decades. The positive effect of sur-
gical treatment was significant – but only at the p<0.05 level (Table 9), indicating that other medical care improvements than surgical treatment must have played their part. Further research should be performed to investigate for instance the effect of biological anti-rheumatic treatment on fracture incidence and survival.

The continuously rising incidence of spinal fractures related to AS – despite the improvements of medical treatment – may be explained by changes in the population age pyramid, greater awareness of fractures, improved diagnostics, improved emergency care reducing fatalities, and a higher activity level of patients receiving modern medical and physical therapy (Caron, Bransford et al. 2010, Robinson, Sandén et al. 2013). For the individual surgeon, this means that the level of alertness cannot be lowered for injured AS patients. An AS patient – even after minor trauma – should be managed as having a fracture until the diagnosis has been established or excluded (Pedersen, Clausen et al. 1987). Preventive measures – as the avoidance of alcohol intoxication, contact sports (i.e. rugby), high impact sports (i.e. tennis), and the use of seat belts and car seat headrests at all times while driving – should not be neglected (Heyde, Robinson et al. 2007). First during the upcoming decades, the optimised biological treatment will have reached a greater epidemiological effect. Until then, hopefully, the increasing trend of spinal fracture incidence related to AS has been reversed.
Study IV

Results

Participants
The original registry extract from the NPR contained 142,073 entries of patients with spinal fractures or AS. Of these 12,297 patients with AS were included. The inclusion flow diagram is depicted in Figure 15.

Descriptive data

Demographics:
291 patients with AS had a fracture between 2011-2014. Patients with fractures were predominately male (ratio 4:1, p<0.001), slightly older (p=0.01), but had a higher CCI (p<0.001) than those without fracture. For 185 patients (64%) the AS was diagnosed at the same time as the first spinal fracture occurred. In 106 patients (36%) the first spinal fracture occurred about 13±8 years after first AS diagnosis was registered in the NPR. (Table 10).

Exposures
About 13% of all patients with AS received bDMARD. Those receiving bDMARD were younger (p<0.001), had less co-morbidity (p<0.001), had rheumatoid arthritis at a higher rate (p<0.001), and received other anti-rheumatic treatment at a higher rate (p<0.001) (Table 11).

Confounders
The AS diagnosis of patients with bDMARD occurred 10±8 years ago, while for those without bDMARD treatment it is 13±9 years ago (p<0.001). Those with bDMARD had a CCI of 2.6±1.9 and those without bDMARD had a CCI of 4.6±2.5 (p<0.001) (Table 11).
Outcome data

AS prevalence and Fracture rate

The prevalence of AS registered in the PDR in Sweden was 8587 in 2014 (0.88 %) with an annual incidence of 5.84 per 100,000 inhabitants in 2014. The annual spinal fracture rate related to AS 2011 to 2014 was 73 patients, implying that every year 0.85 % of patients with prevalent AS will suffer a spinal fracture.

Main results

Prescriptions of anti-rheumatic drugs during the last decade

The number of bDMARD prescriptions increased linearly during the last decade from 4% in 2005 to 11% in 2014 (r=0.99, p<0.001). Simultaneously the proportion of MTX- (r=0.89, p<0.001) and sulfasalazine-treated (r=0.97, p<0.001) decreased. The proportion of patients receiving more than 1 year of anti-rheumatic treatment 2005-2014 is presented in Table 10 and Table 11. Between 2005 and 2014 patients were receiving bDMARD for 4.3±2.9 years, MTX for 3.8±3.0 years, sulfasalazine for 3.9±3.3 years, and NSAID for 5.0±3.0 years.
Fracture free survival and years of bDMARD treatment

1.5% of patients with bDMARD-treatment had a spinal fracture 2011-2014, compared to 2.4% of those without bDMARD treatment (p=0.047). Male gender was most predictive for a spinal fracture 2011-2014 (OR=2.03, 95% C.I.=1.53-2.75, p<0.001), while the amount of years with bDMARD-treatment had a non-significant trend reducing spinal fractures (OR=0.93, 95% C.I.=0.85-1.01, p=0.093) in the most predictive logistic regression model (McFadden pseudo $r^2=0.012$, Hosmer-Lemeshow p=0.004).

A multiple linear regression was calculated to predict age when the first spinal fracture is occurring based on years of bDMARD, MTX, sulfasalazine and NSAID treatment. A significant regression equation was found (F(3,286)= 13.07, p<0.001) with an $r^2$ of 0.11. The patients’ predicted age at first spinal fracture is equal to 72.06 – 1.24 (bDMARD) – 1.31 (sulfasalazine) – 1.04 (NSAID), where bDMARD, sulfasalazine and NSAID are measured in years of treatment. The age for the first spinal fracture decreased 1.24 years.

---

**Table 10: Baseline data of patients with ankylosing spondylitis with and without a spinal fracture between 2011 and 2014.**

<table>
<thead>
<tr>
<th></th>
<th>fracture 2011-2014</th>
<th>no fracture</th>
<th>all</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>n</td>
<td>291</td>
<td>12006</td>
<td>12297</td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td>69</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>sd</td>
<td>14</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>CCI</td>
<td>mean</td>
<td>5.0</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>sd</td>
<td>2.4</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Years with AS</td>
<td>mean</td>
<td>6</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>sd</td>
<td>8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>male</td>
<td>%</td>
<td>80%</td>
<td>66%</td>
<td>67%</td>
</tr>
<tr>
<td>female</td>
<td>%</td>
<td>20%</td>
<td>34%</td>
<td>33%</td>
</tr>
<tr>
<td>SCI</td>
<td>%</td>
<td>7%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>RA</td>
<td>%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>malignancy</td>
<td>%</td>
<td>6%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>bDMARD</td>
<td>%</td>
<td>9%</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>MTX</td>
<td>%</td>
<td>12%</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>%</td>
<td>7%</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>NSAID</td>
<td>%</td>
<td>68%</td>
<td>64%</td>
<td>64%</td>
</tr>
</tbody>
</table>
for every year of bDMARD treatment, 1.31 years for every year of sulfasalazine treatment, and 1.04 years for every year of NSAID treatment. bDMARD, sulfasalazine and NSAID treatment years were significant predictors of age at first spinal fracture.

Patients between 40 and 70 years of age receiving bDMARD had their fracture 2011 to 2014 at a median age of 59 years (95% C.I. 54-62), while those without bDMARD treatment had their fracture at the median age of 62 years (95% C.I. 60-63).

Table 11: Baseline data of patients with and without bDMARD treatment. Presented with p-values of group differences.

<table>
<thead>
<tr>
<th></th>
<th>with DMARD</th>
<th>w/o DMARD</th>
<th>all</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>1324</td>
<td>10973</td>
<td>12297</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>53</td>
<td>69</td>
<td>67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sd</td>
<td>13</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td><strong>CCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>2.6</td>
<td>4.6</td>
<td>4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sd</td>
<td>1.9</td>
<td>2.5</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td><strong>Years with AS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>10</td>
<td>13</td>
<td>13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sd</td>
<td>8</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><strong>male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>64%</td>
<td>67%</td>
<td>67%</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>36%</td>
<td>33%</td>
<td>33%</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>SCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>0%</td>
<td>1%</td>
<td>1%</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>RA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>6%</td>
<td>3%</td>
<td>3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>malignancy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>3%</td>
<td>9%</td>
<td>8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>fracture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>1.6%</td>
<td>2.5%</td>
<td>2.4%</td>
<td>0.048</td>
</tr>
<tr>
<td><strong>MTX</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>46%</td>
<td>9%</td>
<td>13%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Sulfasalazine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>27%</td>
<td>8%</td>
<td>10%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>NSAID</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>88%</td>
<td>61%</td>
<td>64%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Discussion

This study documented a dramatic increase in the prescriptions of bDMARD for patients with AS during the last decade. Furthermore, prevalence and incidence of spinal fractures related to AS have been presented in recent nationwide data. This study failed to identify a significant effect on spinal fracture risk, but established a bDMARD treatment time dependent effect on the age of the occurrence of the first spinal fracture.

Spinal fractures and anti-rheumatic treatment for AS

One of the most recognised complications of AS are spinal fractures, which are associated with multiple potentially hazardous complications (Muñoz-Ortego, Vestergaard et al. 2014). Reason for the susceptibility of the ankylosed spine to fractures are long lever arms of the stiff spine (Robinson, Robinson et al. 2015), as well as osteoporosis related to this rheumatic disease (Carter and Lories 2011).

Since the introduction of bDMARD for anti-rheumatic treatment expectations were high for a reduced disease activity, possibly delaying ankylosis. A radiographical study found reduced progression of spinal ankylosis if patients received bDMARD for more than 4 years (Maas, Arends et al. 2016). The medium-term beneficial effects of bDMARD on the burden of disease of AS are well-documented, and bDMARD are nowadays an important pillar of anti-rheumatic therapy for AS (Braun, van den Berg et al. 2011, Maxwell, Zochling et al. 2015). The availability of national registries for disease, mortality and prescriptions allowed now for the first time an investigation of the anti-rheumatic prescription routine and spinal fracture risk of patients with AS with nationwide coverage. For countries like Germany (Fassmer, Garbe et al. 2016) an increase of prescriptions of bDMARD has been reported during the last decade. A similar trend was found for AS patients in Sweden, which documents adherence to current treatment recommendations.

Nine percent of AS patients with spinal fracture 2011 to 2014 received bDMARD, compared to 13% of those without fracture (p=0.047). These differences were not found for any other anti-rheumatic medication (Table 10). The most predictive model for spinal fracture risk found a trend towards fewer spinal fractures per year of bDMARD treatment (OR=0.93, 95% C.I.=0.85-1.01, p=0.093). The multiple regression analysis of patient with spinal fractures found bDMARD treatment delaying spinal fracture debut by 1.24 years per year of bDMARD treatment. Obviously the beneficial effects on radiographic progression of ankylosis (Maas, Arends et al. 2016) reduced the spinal fracture risk related to the unfavourable biomechanics of AS. Still, these findings are weak and should be interpreted with caution.

Interestingly even other authors found an effect of anti-rheumatic drugs on spinal fracture incidence related to AS. Muñoz-Ortego et al. (Muñoz-Ortego, Vestergaard et al. 2014) presented Spanish national population based registry
data from 2006 in 6474 patients with AS, suggesting regular NSAID-treatment to reduce spinal fracture risk (p=0.02). Unfortunately, they did not include bDMARD-treatment in their analysis. Vosse et al. (Vosse, Landewe et al. 2009) made similar conclusions from a UK General Practice Research Database extract from 1988 to 1999, where NSAID but not sulfasalazine was associated with a reduced spinal fracture rate related to AS (OR 0.65; 95% CI 0.50-0.84). Here, again bDMARD were not investigated, most likely due to the historical data, when bDMARD treatment was not common practice.

**Conclusions**

This study documented for the first time a beneficial effect of bDMARD on spinal fractures related to AS, most likely by delaying the spinal fracture debut. The relatively short available follow-up of 10 years may have underestimated both beneficial and adverse effects of bDMARD. Therefore, follow-up studies on this unique national cohort are recommended to validate the findings in this study.
Study V

Results

Vertebral kinematics

Figure 16 shows the rotations in the sagittal plane of the cranium and C1 to C7 vertebrae for the load 1.5g relative the T4 vertebra. In the following figure, negative value for rotation corresponds to posterior rotation of the vertebra around its own centre of gravity. In other words, the negative value means that the rotation of a given vertebra is causing global extension in the spine. The rotations for the other implant configurations than the C6C7 implant were not included since they were too similar to the C6C7 implant. All the rotations were calculated in relation to the T4 vertebra. Note that the curves representing the non-fracture AS model and the C6C7 implanted model are almost completely overlapping. The same characteristics that can be seen for the 1.5g load case can also be seen for the 3.0g and 4.5g load cases. This figure shows what happens with the movement in the case of the fractured AS model: Movement occurs in the Head-C1 joint, the C1-C2 joint (that are left mobile) and at the C6C7 level (where the fracture is located).

Vertebral gap at fracture site

Figure 17 shows the maximum vertebral gap at the fracture site that occurs during the simulation time. It is shown for all three loads and selected model variations. Increasing load clearly increases the gap regardless of model variation. Note that there is relatively little difference between the different instrumentations. Also note that the implants allow some movement, compared to the non-fractured AS-model.

Translation in fracture

Figure 18 shows the peak value for the horizontal translation at the fracture site, in the transverse plane, for the superior vertebra in relation to the inferior. The translation is shown for all three loads and selected model variations. Increasing load increases the translation. The implant that restricts the movement the most is the C3toT3 configuration for all loads, but the difference is minor. Note that for the load 1.5g, the C6C7 implant allows markedly more movement than the other configurations.
Figure 16: Sagittal plane rotations of head and C1 to C7 vertebrae around their respective centres of gravity for load 1.5g relative T4. Note that the curve for the implanted model (green) overlaps the “AS no fracture” (blue) curve.
Figure 17: Maximum fracture site vertebral gap for the different loads and implant variations

Figure 18: Maximum horizontal translation in fracture. AS conditions in all cases.
Maximum stresses in the disc ossifications

In order to get an overview of the stresses over time, Figure 19 shows the peak value that occurs in the ossified part of the discs during the simulation, for the three load cases. The C6C7 disc level is not included since the ossified part was removed to simulate the fracture at that level.

Consider first the pillar representing the C5toT1 implant: Note that for the C5C6 and C7T1 disc levels, the stresses are reduced compared to the adjacent C4C5 and T1T2 disc levels. The C5C6 and C7T1 levels are also those that are inside the range of that specific implant.

A similar deload also occurs for the two longer implants (C3toT3 and C3C6C7T3), that both end at the C3 vertebra, which is: The implant deloads the disc ossifications that are inside the range of the implant. Note also that the stresses for the C2C3 disc levels for these implants are at the same level as the non-fractured AS-model. Furthermore, when studying the stresses in the ossifications in the discs in the thoracic spine (T2T3, T3T4, T4T5), the stresses are notably lower in general than they are in the cervical spine. However, the largest stress overall appears in the T1T2 level which is the first disc in the thoracic spine.

Figure 19: Peak value of first principal stress in the ossification at different disc levels.
Discussion

This study provides for the first time results from a biomechanical model supporting the current surgical practice of long posterior stabilization of spinal fractures related to AS. Major findings with regard to posterior cervicothoracic instrumentation were (1) an improved stability with increasing length of the construct, (2) no significant reduction of construct stability of levels were skipped in the instrumentation, (3) reduced stress of the instrumentation’s cranial end segment if levels were skipped.

Limitations of this study

One major limitation of this study is the simplification of the spine in AS. Typical features as kyphosis and regional osteoporosis are highly individual and therefore hardly to include in this simplified model. In order to have a more realistic model CT scans of patients with AS could be converted into FE models, which then include patient-specific deformity and osteoporosis. Cadaveric CT based FE models have recently been developed for the lumbar spine (Campbell, Coombs et al. 2016), but their application in patients is ethically questionable with regard to the relatively high radiation exposure of computed tomography (Richards, George et al. 2010).

Furthermore, validation of the FE model is complicated by the fact that until now no established cadaveric models of the ankylosed spine exist (Jones and Wilcox 2008). Thus this model is based on empirical assumptions, which are logically deducted from current knowledge but not biomechanically validated.

Beyond that, the single unidirectional impulse model of our study is insufficient to test stability of posterior instrumentation for realistic conditions, where multicyclic loads may lead to implant failure (Edwards 1991).

The screw-bone interface used in this study has no sufficient resolution for pull-out analysis of instrumentation. In order to simulate screw pull-out, this has to be modelled in a simulated osteoporotic vertebra with a high-resolution model of an implant model in place. Similar designs have been successfully performed in previous studies (Chatzistergos, Magnissalis et al. 2010).

The material properties of the elements representing the ossified parts of the discs were given linearly elastic and isotropic properties. In reality, bone is more complex and has anisotropic and time-dependent properties. However, this was not considered in this study. If the time dependent properties were to be introduced, then the results would depend more on the chosen load scenario. Also, there would probably not be the linear increase in for example fracture gap at increased load that can be seen in this study.

Construct length for posterior spinal instrumentation

The optimal method of stabilisation of spinal fractures related to AS is a matter of debate. Most authors agree on surgical treatment with long constructs
(Robinson, Robinson et al. 2015, Robinson, Willander et al. 2016), even though non-surgical treatment has been proposed by some authors as possible alternative (Altun and Yuksel 2016). Opinions diverge on the necessity of additional anterior fixation in order to stabilise the anterior column.

Since no authors have investigated spinal fixation of AS related fractures in a biomechanical model, the findings of this study are the best available evidence for stabilisation. Prior to generalisation our findings have to be validated in clinically relevant settings. This will be matter of further research.

**Skipped level instrumentation**

The concept of skipped levels has been previously applied in spinal deformity surgery and in long bone fracture fixation. Increased implant density was associated with proximal junctional kyphosis in adult deformity surgery (McClendon, Smith et al. 2016). Besides screw-malplacement issues, the extra costs of unnecessary screws could increase cost-effectiveness of spinal instrumentation (Larson, Polly et al. 2016). The presented model was not sufficient to determine a significant difference in the stress on adjacent segments, but indicated no increased fracture displacement risk with fewer screws.

**Conclusion**

This study tested a modified previously validated FE model of the cervical and thoracic spine to simulate a spinal fracture related to ankylosing spondylitis. The suggested FE model has to be validated, and will be subject of future research. This study could be considered a starting point for how a finite element model of the spine can be used to investigate the effect of spinal implants in the case of a fracture in an AS-spine.
General discussion

The above presented studies had following main findings: (1) Spinal fractures are a common complication to trauma in patients with AS. (2) Despite the improved medical therapy including the growing use of bDMARD the incidence of spinal fractures increased during the last two decades. (3) Surgical treatment of these fractures improves survival but is associated with severe complications. (4) Finite element models could be used to analyse spinal stabilisation of fractures related to AS.

Limitations

Following limitations of registry studies have to be taken into consideration:

(1) *An observational error*, meaning a systematic bias during data collection. Missing information at the time of admission due to communication failures, the surgeon’s defect knowledge, or the surgeon’s lack of attention to detail, reduce the quality of registration (O’Malley, Cook et al. 2005). Beyond that, poor coder training, absent quality control, misspecification, unbundling, and upcoding lead to inappropriate registration of correctly written diagnoses (O’Malley, Cook et al. 2005).

(2) Fracture underreporting may occur while prehospital fatalities are not registered in the SPR, and causative AS-related spinal fractures remain unrecognised (Alker, Oh et al. 1975). The diagnosis registration of deceased patients during or right after treatment is most likely not pursued with the same endeavour as of those discharged in a healthier condition.

(3) *Improved diagnostics* identify earlier and more accurately AS. In the NPR a relatively unchanged annual incidence of ankylosing spondylitis was seen until 2000. From 2001 onward a significant linear increase was found, suggesting either a greater spread of the disease, or - rather more likely – improved diagnosis of AS. The greater implementation of the ASAS-criteria for diagnosis of AS allowed a more standardised and homogenous identification of the disease (Wolf and Fasching 2011).
(4) *The changes in the diagnostic criteria for AS* during the last decade from the modified New York criteria to Assessment of Spondyloarthritis International Society (ASAS) criteria could have led to a gradual change in the demography of registered AS patients (Robinson and Benham 2015). Interestingly, in our cohort in study IV most patients (64%) received their first AS diagnosis in conjunction to their first spinal fracture. These patients did not appear in registries despite their obvious disease, implying that two thirds of our AS patients remain undetected even with the updated diagnostic criteria.

(5) *Overestimation of medication expenditure.* Prescription and expenditure registered in the PDR does not mean that the patient took his medication. There is abundant data that patients only take about 50% of their prescribed medication (Brown and Bussell 2011). Since bDMARD are administered subcutaneously, it is monitored more closely by the GP or by the rheumatologist than other drugs. Thus the effect of this bias with regard to bDMARD treatment should be minimal.

(6) *Regional differences in the accessibility of health care* in Sweden could delay the primary diagnosis of AS. These data were not included in the registry extract of our study.

(7) *Population bias.* The national registry data represents the geographically, health-economically and ethnically specific population in Sweden, which cannot be generalised to other countries’ populations. Future studies from national prescription registries in other countries will have to validate our results in their unique setting.

(8) Results of registry studies are prone to the *selection of an inadequate reference group.* It is very likely that those receiving treatment (surgery, or bDMARD) have greater access to high quality healthcare and were possibly screened for AS at an earlier age, thus receiving adequate physiotherapy and prevention, while those with less access were possibly diagnosed with AS together with their first spinal fracture when medical treatment is not an option anymore. Thus, bDMARD treatment or surgical treatment possibly adds to best practice AS care, while the reference group implies more or less a natural history of disease progression.

(9) There is even a *selection bias* where patients with bDMARD treatment have a more therapy resistant form of AS and thus receive this still expensive treatment. Those without bDMARD were then relatively symptom free with NSAID treatment. Thus bDMARD treatment could be associated with a more aggressive course of the disease, biasing the bDMARD group towards worse results. If baseline and outcome measures would have been included in the parametrically
adjusted models this bias could be minimised. The growing availability of health related quality of life data will enable these study designs in the near future.

(10) One major limitation of the study on bDMARD treatment effects is the relatively short observation time for the medication data, which is only available since 2005. Since a long-term effect of anti-rheumatic treatment is to be assumed, longer observation periods of this cohort could change the presented results. Therefore, it is mandatory to revisit this cohort in the future to audit our assumptions based on medium-term follow-up.

The validation of the NPR using other quality registries confirms high validity of registered orthopaedic diagnoses (Ludvigsson, Andersson et al. 2011). Diagnoses as hip fractures are correctly identified in more than 95%. Since the NPR was started in the 1960s, a coding learning curve could explain an increasing incidence for most diagnosis groups. Instead no increasing incidence of lumbar fractures was reported in the NPR during the last decades, which would have been expected if a systematic bias was present (Robinson, Sandén et al. 2013). Obviously the current registration quality is good, and registration bias cannot explain the findings in this study. Besides, the Swedish reimbursement policy requires complete diagnosis registration, an effective incitement to proper coding.

Multiple limitations specifically for the discovered increasing incidence of spinal fractures related to AS have been discussed:

(1) Improved survival of patients suffering from unstable vertebral fractures. The meta-analysis of Westerveld et al (Westerveld, Verlaan et al. 2009) found an overall mortality of 17.7% within the first three months after a vertebral fracture in AS, being 6.4% in the operatively treated and 11.3% in the non-operatively treated subgroup (n.s.). Optimised acute treatment during the last decades may have led to improved survival directly after injury, leading to more hospital admissions being registered in the National Patient Register.

(2) An increasing level of activity with a reduced safety profile and greater risk for injuries of AS patients. Multiple medical treatment strategies as well as physiotherapy interventions have been found to improve function and reduce stiffness in AS (Dagfinrud, Kvien et al. 2005, Goh and Samanta 2009). Unfortunately, once the biomechanical flexibility of the spine is declining, these still very active patients are prone to injuries, possibly leading to a greater number of spinal fractures (Heyde, Robinson et al. 2007).

(3) Patients with AS have possibly a prolonged life span nowadays due to improved therapy. This would cause an increasing population with AS due to reduced mortality. This hypothesis is supported by the finding
that the number of registered patients with AS increased during the observed years.
Conclusions

I. During the last two decades an increase in the incidence of vertebral fractures in patients with AS could be observed in Sweden.

II. We could demonstrate that posterior stabilisation is an effective method in regaining stability without the necessity of additional external fixation, while complications are common during the postoperative course.

III. Surgical treatment improved survival after spinal fractures related to AS. This should lead to stronger recommendations to treat these spinal fractures related to AS surgically.

IV. We could provide for the first time evidence of a beneficial effect of bDMARD with regard to spinal fracture occurrence. The risk of spinal fractures was not reduced, but the debut of a spinal fracture was delayed with bDMARD. Since for this study the observation interval was only a decade, a follow up in the future will most likely reflect the effect of bDMARD even more.

V. Using a finite element model spinal fractures related to AS could be simulated, and their stabilisation could be tested using posterior instrumentation models.
Clinical implications

The above presented study results have following important clinical implications:

1. Surgical stabilisation should be the recommended treatment for spinal fractures related to AS since it reduces mortality.
2. When instrumenting patients with spinal fractures of the cervicothoracic junction complications should be anticipated and prevented.
3. bDMARD treatment is beneficial for patients with AS not only with regard to health related quality of life but also with regard to spinal fractures.
4. Surgeons should consider to reduce the amount of screws, but not construct length, while stabilising spinal fractures related to AS, which would reduce implant-related risks and costs.
Summary in Swedish – sammanfattning på svenska

Kotfrakturer vid mb Bechterew – Epidemiologi, kliniska resultat och biomekanik

Mb Bechterew (ankyloserande spondylit, AS) är en reumatisk sjukdom som leder till en progressiv förbening av hela kotpelaren. På grund av den multi-segmentella förbeningen, osteoporos och den ökade fallrisken vid mb Bechterew, är kotfraktur en vanlig komplikation.

Denna avhandling sammanfattar incidens, behandling, komplikationer och mortalitet vid kotfrakturer hos patienter med mb Bechterew. Biologiska sjukdomsmodulerande antireumatiska läkemedels (bDMARD) effekt på kotfrakturrisken utvärderas dessutom.

Patientregistret, dödsorsaksregistret och läkemedelsregistret har sammanlänkats för att hitta prediktorer för mortalitet och kotfrakturer. Med en finite element modell (FEM) har vi kunnat simulera en kotfraktur vid mb Bechterew.


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