Axis Fractures in Elderly

Epidemiology and Treatment related outcome

ANNA-LENA ROBINSON
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Abstract

Background: Axis fractures are a common injury in the elderly population. Treatment is often complicated due to osteoporosis and patient comorbidity. Knowledge of the incidence of these fractures, as well as their treatment, outcome and mortality rate, will improve knowledge and decision-making processes for this fragile group of patients.

Objectives: This thesis aims (1) to review the literature on the non-surgical and surgical treatment of odontoid fractures type 2 in the elderly population, (2) to provide an updated overview of axis fracture subtypes, their incidence and their treatment in a cohort in two university cities, (3) to map the incidence of fractures and the treatment of these patients in Sweden, (4) to investigate the effect on mortality of both the surgical and non-surgical treatment of axis fractures and (5) to present the protocol for a randomized controlled trial (RCT) on the treatment of odontoid fractures type 2 in the elderly population.

Methods: A systematic review was performed using the MeSH keywords “odontoid AND fracture AND elderly”. The data for the cohort study were extracted from the regional hospital information system. The radiographs were reviewed retrospectively. Data were extracted from the Swedish National Patient Registry (NPR) and the mortality registry for the national registry studies. Finally, the RCT protocol was carried out according to the SPIRIT and CONSORT statements for clinical trial reporting.

Results and conclusions: So far, there has been a scarcity of existing evidence on treatment of odontoid fractures type 2 in the elderly population. In this thesis, we found in two university cities an increased incidence, and a trend towards more surgical treatment of type 2 and 3 odontoid fractures 2002-2014. Between 1997 and 2014 in Sweden, there was an increasing incidence of C2 fractures, but the treatment trend went towards more non-surgical treatment. Surgically treated patients had a greater survival rate than non-surgically treated patients. Among those over 88 years of age, surgical treatment lost its effect on survival. In the RCT we will study the function of patients with odontoid fractures type 2 and by comparing non-surgical treatment with posterior C1-C2 fusion, the cost-effectiveness of the treatment options.

Keywords: odontoid fracture, treatment, elderly, cervical spine, axis fracture

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To All Strong Women
List of Papers

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

I

Robinson, Y., Robinson, A.-L., and Olerud, C.
Systematic Review on Surgical and Nonsurgical Treatment of Type II Odontoid Fractures in the Elderly.

II

Robinson, A.-L., Möller, A., Robinson, Y., and Olerud, C.
C2 Fracture Subtypes, Incidence, and Treatment. Allocation Change with Age: A Retrospective Cohort Study of 233 Consecutive Cases.

III

Robinson, A.-L., Olerud, C., Robinson, Y.

IV

Robinson, A.-L., Olerud, C., Robinson, Y.
Surgical treatment improves survival of elderly patients with axis fracture – a national population-based multi-registry cohort study. *Submitted manuscript*

V

Robinson, A.-L., Schmeiser, G., Robinson, Y., Olerud, C.
Protocol for a multicentre randomised controlled trial on displaced odontoid fractures type 2 in patients aged ≥75 years: The Uppsala Study on Odontoid Fracture Treatment (USOFT). *Submitted manuscript*

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Abbreviations

C#  Cervical vertebra no. #
CCI  Charlson Comorbidity Index
CT  Computed Tomography
CDR  Swedish Cause of Death Registry
CI  Confidence Interval
CONSORT  Consolidated Standards of Reporting Trials
EQ-5D  EuroQol group
ICD-10  International Classification of Diagnosis
GRADE  Grading of Recommendations, Assessment, Development and Evaluations
HR  Hazards Ratio
HRQoL  Health related quality of life
ITT  Intention to Treat
MCID  Minimal Clinically Important Differences
MeSH  Medical Subject Heading
MRI  Magnetic Resonance Imaging
NDI  Neck Disability Index
NPR  National Patient Registry (Sweden)
p  Statistical probability
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<td>RR</td>
<td>Risk Ratio</td>
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<td>RRR</td>
<td>Relative Risk Reduction</td>
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<td>$\chi^2$ test</td>
<td>Chi squared test</td>
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<td>SNOSE</td>
<td>Sequentially Numbered, Opaque Sealed Envelopes</td>
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<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
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<tr>
<td>USOFT</td>
<td>Uppsala Study on Odontoid Fracture Treatment</td>
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<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
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</table>
Axis fractures are the most common cervical injury among the elderly population, but they are also common among the young and active population (Anderson and D’Alonzo 1974). Between 9% and 18% of cervical fractures are C2 fractures, according to earlier publications. Fractures of the second vertebrae (C2 fractures) can be divided into odontoid fractures type 1, 2 and 3, Hangman’s fractures type 1, 2 and 3, and atypical C2 fractures (Anderson and D’Alonzo 1974, Edward C. Benzel, Blaine L. Hart et al. 1994, Kandziora, Schnake et al. 2010). C2 fractures comprises between 35 and 78% of odontoid fractures, Hangman’s fractures between 11 and 25% (Hadley, Dickman et al. 1989, Ryan and Taylor 1993, Greene, Dickman et al. 1997), and atypical fractures between 14% and 20% (Hadley, Dickman et al. 1989, Greene, Dickman et al. 1997).

The distribution of the various fracture types differs between younger and older patients, since C2 fracture types are associated with different fracture mechanisms (Greene, Dickman et al. 1997). While younger patients who have suffered a C2 fracture are injured in high energy accidents, the elderly usually sustain bone density-related injuries. (Brolin and von Holst 2002) Osteoporosis, as well as a stiff lower neck among the elderly population, increases the risk of injuries in the upper part of the cervical spine (Ryan and Taylor 1993, Lomoschitz, Blackmore et al. 2002). The most common C2 fracture, the odontoid fracture, has a biphasic distribution and occurs most in 20-30-year-old and 70-80-year-old patients; as mentioned above, they are related to different types of trauma mechanism (Brolin and von Holst 2002).

Computed tomography (CT) is the most reliable radiographic tool for classifying the fracture type and evaluating the healing of C2 fractures (Koller, Kolb et al. 2009).

The treatment of axis fractures varies, depending on the fracture type and the patient’s age, from external fixation with a rigid cervical collar and halo-vest treatment (Lind, Nordwall et al. 1987, Seybold and Bayley 1998, Stoney, O’Brien et al. 1998, Murphy, Schroeder et al. 2017), to surgical treatment by anterior direct osteosynthesis, anterior fusion, and posterior fusion (Suchomel, Hradil et al. 2006, Dailey, Hart et al. 2010, Aldrian, Erhart et al. 2012, Bourdillon, Perrin et al. 2014). For example, in the younger population, the most common treatment for odontoid fractures type 2 is anterior screw osteosynthesis, while the best treatment option for the elderly population has been
debated and no high evidence studies are available. Recent treatment recommendations for the elderly vary widely across the globe; there are probably also regional differences within Sweden.

There have been signs of an increased incidence of axis fractures among the elderly, as well as a growing elderly population (European commission 2014). Along with this increased incidence of fractures, a growing number of clinical studies have indicated that the surgical stabilization of odontoid fractures type 2 is leading to improved fracture healing and survival (Chapman, Smith et al. 2013), although surgery is associated with peri- and postoperative complications, which could outweigh the benefits of surgical treatment (Patel, Zakaria et al. 2015, Deng, Yue et al. 2016).

**Classification**

C2 fractures can be divided into odontoid fractures, Hangman’s fractures and atypical fractures.

**Odontoid fractures**

The fracture mechanism is the hyperextension or hyperflexion of the cervical spine (Müller, Wick et al. 1999, Pal, Sell et al. 2011).

Odontoid fractures are classified according to Anderson and D’Alonzo, (Anderson and D’Alonzo 1974), where type 1 is a rare fracture in the tip of the odontoid process above the level of the cruciform ligament (Figure 1a-b); type 2, a fracture in the base of the odontoid process below the level of the transverse band of the cruciform ligament (Figure 1c-d); and type 3 runs through the axis body into the lateral mass of C2 (Figure 1e-f).

In 2005, Grauer et al. proposed a modified, treatment-oriented classification of odontoid fractures. The modified classification distinguishes between odontoid fractures type 2 and shallow type 3, where a type 3 fracture should be considered if the fracture line runs through, and extends laterally into, the C1-C2 joint (Grauer, Shafi et al. 2005) (Figure 2). Further, they proposed sub-classifications of odontoid fracture type 2 patterns to facilitate surgical approach decisions.

An odontoid fracture type 2 is considered displaced and more unstable when there is a 5-mm anterior translatory displacement, any posterior translatory displacement or 10° of angulation (Greene, Dickman et al. 1997, Koivikko, Kiuru et al. 2004, Grauer, Shafi et al. 2005, Osman, Alageli et al. 2017). Displacement is measured on a cervical spine reconstruction CT scan.
Odontoid fracture classification

Type 1

Figure 1: Odontoid fracture classification according to Anderson and D'Alonzo.

Type 2

Type 3

Figure 2: Differentiation of odontoid fracture type 2 and type 3 according to Grauer. A type 3 fracture runs through the articular facets of C2.
Hangman’s fractures

Hangman’s fractures are characterized by traumatic spondylolisthesis of the axis caused by bilateral fractures of the pars interarticularis. The fracture mechanism is a primary axial compression and hyperextension leading to a fracture of the pars interarticularis/the pedicles, followed by a flexion of the cervical spine that tears the posterior longitudinal ligament and the C2-C3 disc. On the other hand, the opposite mechanism is a primary hyperflexion, followed by a secondary extension (Ferro, Borgo et al. 2012).

In 1981, Effendi et al, proposed a classification of Hangman’s fractures based on radiological displacement and stability. Type 1 is a non-dislocated fracture of the ring of the axis caused by mild hyperextension and axial loading (Figure 3a). Type 2 is a displaced fracture caused by hyperextension and secondary flexion resulting in a pedicle fracture, dislocation of ≥3 mm and a rupture of the C2-C3 disc (Figure 3b). Finally, in the rare Hangman’s fracture type 3, the body of the C2 disc is in flexion and the facet joints are dislocated and locked. The fracture mechanism is a hyperflexion followed by a rebound extension (Figure 3c). (Ferro, Borgo et al. 2012)

The Effendi classification has been modified by Levine and Edwards, who included the trauma mechanism in their classification, as well as a complementary fracture type, type 2a; this has a greater angulation and not much translation. In type 2a fractures, the trauma mechanism is flexion-distraction (Levine and Edwards 1985).
Hangman’s fracture classification

Type 1

Type 2

Type 3

Figure 3: Hangman's fracture classification according to Effendi.

Atypical fractures

Atypical fractures in the axis are rare. They have been classified by Benzel et al. into type 1 fractures with a mainly coronal orientation of the fracture line, type 2 with a sagittal fracture line and type 3 with a predominantly horizontal fracture orientation (Benzel, Hart et al. 1994).
Treatment

Odontoid fractures

Odontoid fractures type 1 are extremely rare fracture, and the treatment should be according to the associated ligamentous injury. Since a type 1 fracture could be an indirect sign of occipito-cervical dissociation, a magnetic resonance imaging (MRI) is necessary, especially if non-surgical treatment is planned. Odontoid fractures type 3 are considered stable fractures and are treated non-surgically with a well-fitting rigid cervical collar, such as the Philadelphia collar (Össur, Sollentuna, Sweden) or the Aspen collar (Aspen Medical Collars, Irvine, USA). The collar should be worn 24 hours a day for 12 weeks (Muller, Schwinnen et al. 2003).

Odontoid fractures type 2 can be treated non-surgically with a rigid cervical collar or halo-vest (Lind, Nordwall et al. 1987, Patel, Zakaria et al. 2015, Osman, Alageli et al. 2017), or surgically with an anterior lag screw fixation or posterior C1-C2 fusion. The anterior fixation, according to Böhler, is a common treatment for younger patients, where there is no osteoporosis or concomitant atlantoaxial joint injury (Bohler 1982, Andersson, Rodrigues et al. 2000) (Figure 4). Even though commonly applied even in elderly, results of anterior screw osteosynthesis in elderly patients are complicated by the prevalent comorbidity (Przkora, Robinson et al. 2006). The anterior screw approach is relatively contraindicated in patients with an upwards oblique fracture line. With patients with cervical kyphosis and obese patients, it is also difficult to correctly position the screws using an anterior approach (Nourbakhsh, Shi et al. 2009).

![Figure 4: Anterior odontoid lag screw osteosynthesis according to Böhler.](image-url)
Posterior fusion techniques are preferable in the elderly, more osteoporotic population. These techniques involve transarticular C1-C2 screws, according to Magerl, as well as the C1 claw device or the Gallie fusion (Gallie 1939, Olerud, Lind et al. 1999, Olerud and Olerud 2001) (Figure 5).

Figure 5: Posterior C1-C2 fusion with Magerl screws and C1 claw device.

Other techniques may also be used, e.g., C1 screws according to Goel-Harms (Harms and Melcher 2001, Goel, Desai et al. 2002) (Figure 6), or translaminar C2 screws as proposed by Wright (Wright 2004). The latter techniques are most often used in cases of anatomical aberrations or a concomitant C1 arch fracture. The posterior surgical techniques proposed by Magerl and Goel-Harms will be described in detail below.

Figure 6: Posterior C1-C2 fusion with a) Judet screws in C2 b) Goel-Harms screws in C1.

The treatment of odontoid fractures type 2 in elderly patients has been debated the last decades. Some authors advocate the use of a rigid collar, as the comorbidity of elderly patients outweighs the benefits of surgical treatment (Osman, Alageli et al. 2017), (Patel, Zakaria et al. 2015); other authors find that surgical alternatives are more suitable for these patients (Omeis, Duggal et al. 2009). Over the last couple of decades, in a North American retrospective cohort, the
treatment trend for odontoid fractures type 2 has favoured surgery (Smith, Vaccaro et al. 2008).

There is no available high-evidence research in this area; moreover, most of the research available focuses on bone healing and not functional outcome.

**Surgical techniques**

*The Magerl technique and the C1 claw device*

The patient is placed prone on the operating table. The head is firmly attached to a head clamp, e.g., a Mayfield clamp, or a skull traction apparatus combined with an adjustable head support. The C1-C2 articulation is reduced to a physiological alignment, which includes the correct extension-flexion position. A C-arm is used to evaluate the possibility of placing Magerl screws across the C1-C2 articulation by placing a straight K-wire lateral to the neck of the patient and correcting the position of the patient accordingly (Figure 5).

A mid-line exposure is centred over the C1-C3 spinous processes. The C1 arch and the upper portion of the C2 spinous process are exposed, including the atlantoaxial membrane. The upper margin and medial border of the C2 arch is exposed all the way to the C1-C2 joints. Correct entry points are chosen for the Magerl screws in the C2 lateral masses, and the screws are placed with aid of the C-arm. The percutaneous entrance site for the drill lies approximately 2 cm lateral to the T1 spinous process (Mummaneni and Haid 2005). The C1 claw device is then firmly attached to the C1 arch and connected to the protruding Magerl screws. The C1 arch and the upper portion of the C2 spinous process are decorticated and an autologous iliac crest bone graft is placed (Cornefjord, Henriques et al. 2003). If the Magerl screws have a good transarticular position, the patient can be mobilized without the application of a collar. In Figure 7 and Figure 8 representative cases for the C1 claw construct are presented.
Figure 7: 81-year-old man hits his forehead in a beam. **a,b**: CT scan shows an odontoid fracture type 2. **c**: Planned for surgery with a Magerl screw and C1 claw device. **d,e**: The postoperative CT scan confirms trans-articular Magerl screw and a good fit of the C1 claw device. **f**: At 1 year follow-up both, posterior fusion and odontoid fracture healed.

Figure 8: 83-year-old man tripped on a carpet and fell backwards. **a**: CT scan shows an odontoid fracture type 2, with no bone abnormalities and no concomitant fracture in C1. **b-e**: Postoperative CT shows good trans articular positioning of the Magerl screws. **f**: 3D CT-reconstructions confirm optimal C1 claw position. **g-i**: At 3 years follow-up, the CT scan shows posterior C1-C2 fusion and no implant loosening.
The Goel-Harms technique

If it is not possible to insert Magerl screws, i.e., if the angulation of the screw insertion is too steep or there are bone abnormalities, or if it is not possible to apply the C1 claw device (i.e. a fractured C1 arch), then the Goel-Harms screw technique is an option.

The entry point for the insertion of the C2 isthmus screw (Judet screw) (ElMiligui, Koptan et al. 2010) is carefully chosen and the screw is placed with aid of the C-arm. The screw direction should be 30° upward and 20° convergent (Figure 6).

The entry point of the Goel-Harms C1 screw requires the retraction of the venous plexuses and the C2 root. The medial and lateral borders of the C1 body are palpated and the screw is placed pointing about 20° upward and 10° convergent (Harms and Melcher 2001, Bourdillon, Perrin et al. 2014) (Figure 6). Rods connect the C1 and C2 screws, and the C1 arch and the upper portion of the C2 spinous process are decorticated and an autologous iliac crest bone graft is placed.

Figure 9 shows a representative case for the Goel-Harms-construct.

*Figure 9: A 70-years old patient fell in his home and was found in the morning. Clinically he presented initially with neck pain, but developed progressive proximal arm paresis within a few hours. a, b: CT scans show a C1-C2 dislocation. c: The T2 MRI visualised the cord compression with central cord oedema. d, e: After C1-C2 fixation according to Goel-Harms the patient’s neurology recovered within 2 weeks. f: The 3-year follow-up reveals a successful fusion and a healed odontoid fracture.*
Hangman’s fractures

Hangman’s fractures type 2 and 3 are most often treated non-operatively with a rigid cervical collar, such as the Philadelphia collar (Össur, Sollentuna, Sweden) or the Aspen collar (Aspen Medical Collars, Irvine, USA). The collar should be worn 24 hours a day for 12 weeks (Ferro, Borgo et al. 2012, Murphy, Schroeder et al. 2017). A halo-vest treatment is an alternative non-surgical option.

Surgical treatment varies from anterior discectomy and C2-C3 fusion, to posterior C1(C2)-C3 fusion. The anterior fusion option is preferable in the case of a traumatic disc herniation (Xu, Zhao et al. 2010) (Figure 10); it also provides a solid bone fusion, which is not always obtained through posterior surgery.

Figure 10: Anterior C2-C3 fusion with anterior plating and bone transplant from the hip.

Complications of non-surgical and surgical treatments

Treatment with a rigid collar is considered a safe option when treating stable cervical fractures, but there can be major complications with non-surgical approaches, including inactivity leading to pneumonia, upper respiratory tract problems, a higher risk of non-union and, as some authors have even found, a greater risk of mortality in type 2 odontoid fracture patients (Koivikko, Kiuru et al. 2004) (Vaccaro, Kepler et al. 2013).

The halo-vest treatment is considered intolerable for elderly patients and has a high risk not only of non-union, but also of pin-site infection or loosening, osteomyelitis, penetration of the dural sac, respiratory function impairment, dysphagia and loss of reduction (Garfin, Botte et al. 1986, Glaser, Whitehill et al. 1986, Koivikko, Kiuru et al. 2004, Majercik, Tashjian et al. 2005, Tashjian, Majercik et al. 2006).

The complications of the anterior surgical approach are non-union, oesophageal or pharyngeal perforation, obstruction of the airway and injury to the vessels or to the glossopharyngeal and hypoglossal nerves (Nourbakhsh, Shi et al. 2009).
The risk of non-union is greater in elderly patients, or if the displacement exceeds 4-6 mm or there is a posterior displacement of the fracture (Greene, Dickman et al. 1997, Nourbakhsh, Shi et al. 2009).

Posterior fusion has another plethora of mainly vascular or neural complications. With the Magerl screw technique, there is a risk of vertebral artery injury if there is a bone aberration of the axis. The C1 screw could harm the vertebral artery if deviated laterally. A laterally placed C1-claw, or a C1-screw placed according to Tan et al. (Tan, Wang et al. 2003) could injure the vertebral artery, if hidden behind the anatomical variation of a posterior ponticle (Young, Young et al. 2005). The C1 screw used in the Goel-Harms can lead to damage of the C2 nerve root and bleeding in the vertebral artery (posterior ponticle) or the venous plexus covering the entrance of the screw. Both the Magerl and Goel-Harms techniques can lead to the compression of the C2 nerve root.

Non-union is also common in posterior fusion, but a fusion rate of 90-100% has been reported for the Goel-Harms method (Scheyerer, Zimmermann et al. 2013) However, non-union should not always be considered a bad outcome, as radiographic non-union is not associated with a worse functional outcome (Molinari, Dahl et al. 2013, Smith, Kepler et al. 2013). In odontoid fractures type 2, fibrosus healing is most often considered sufficient (Muller, Schwinnen et al. 2003, Butler, Dolan et al. 2010).
Aims

This thesis aimed to establish the current evidence on treating elderly patients with a type 2 odontoid fracture, with regard to survival, non-union and complications, in a systematic review (Study 1), as well as to investigate the distribution, incidence and treatment of C2 fractures in a well-defined cohort in two university cities (Study 2). The aims were also to investigate the incidence of fractures and their treatment in Sweden using the Swedish National Patient Registry (Study 3) and to investigate the mortality rate of C2 fracture patients ≥70 years in Sweden by cross linking the mortality register with the Swedish National Patient Registry (Study 4). Finally, the thesis aimed to perform a randomized controlled trial (RCT) on the treatment of type 2 odontoid fractures. The RCT will investigate whether there are any differences in the surgical and non-surgical results of odontoid fractures in the elderly population, with the Neck Disability Index (NDI) score as the primary endpoint and the visual analogue scale (VAS) and Euroqol (EQ-5D) scores as the secondary endpoint in a one year follow-up. By studying the health-related quality of life (HRQoL) and function of patients with type 2 odontoid fractures, while also comparing the outcomes of non-surgical and surgical treatment (posterior C1-C2 fusion), we can address the cost-effectiveness of the treatment options. In this thesis, the study protocol for the RCT is presented (Study 5).
Methods

Study I - Systematic Review of the Surgical and Non-Surgical Treatment of Odontoid Fractures Type 2 in the Elderly

A systematic review was performed using the MeSH keywords “odontoid AND fracture AND elderly”. The search was performed in the following order: NLM (PubMed MEDLINE), Ovid MEDLINE and ISI Web of Knowledge. The quality of the articles was graded according to GRADE criteria (Table 1) (Atkins, Best et al. 2004).

Table 1: Definitions of evidence quality according to GRADE criteria

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<th>Level</th>
<th>Description</th>
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<tr>
<td>High</td>
<td>Further research is unlikely to change our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain.</td>
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Included in the review were the treatment of acute odontoid fractures type 2, non-surgical and/or surgical treatment, studies with > 10 patients (including both younger and elderly patients), elderly (>60 years) patients identified or analysed separately, radiographic and/or clinical and/or survival data, and publications between 1985 and 2013.

These clinical important questions were addressed in this systematic review:

1. Does surgical stabilisation of odontoid fractures type 2 in elderly improve patient survival?
2. Which stabilisation method has the greatest success with regard to type II odontoid fracture healing?
3. Is odontoid non-union associated with worse clinical results than radiographically healed fractures in the elderly?
4. What is the complication rate of nonsurgical treatment compared to surgical treatment of odontoid fractures type 2 in the elderly?
Statistics

A probability of $p < 0.05$ was regarded as statistically significant. Mean values were presented ± the standard deviation. The Kaplan-Meier method was used to determine the mean survival rates of non-surgical and surgical treatment. The Cox regression method was used to determine covariates of survival, with the hazard ratio (HR) presented with 95% confidence interval (CI) and probability $p$. Surgical treatment and age were identified as relevant covariates for survival. Authors of the publications included in the systematic review were asked for the original survival tables if these were not available in the published scientific articles.

The statistical analysis was performed with the Statistical Package for Social Sciences (SPSS Statistics 21.0, IBM Corp., Armonk, NY).
Study II - C2 Fracture Subtypes, Incidence and Treatment. Allocation Change with Age: A Retrospective Cohort Study of 233 Consecutive Cases

All patients treated at two university hospitals in Sweden (Uppsala County and Malmö City) between January 2002 and December 2014 and diagnosed with a C2 fracture (ICD-10: S12.1) were extracted from the regional hospital information system. ICD-10: S12.1 is a fracture of the second cervical vertebrae.

The radiographs were reviewed retrospectively and classified into odontoid fractures type 1, 2 and 3, Hangman’s fractures type 1, 2, and 3 and atypical C2 fractures (Figure 1, Figure 3). No further sub-classification was made of Hangman’s fractures or atypical fractures, as the number of patients was low. To separate shallow odontoid fractures type 2 from odontoid fractures type 3, Grauer’s modified classification was used (Figure 2). The modified classification distinguishes between odontoid fractures type 2 and shallow type 3, where a type 3 fracture should be considered if the fracture line runs through, and extends laterally into, the C1-C2 joint surface. The odontoid fractures type 2 and 3 from Uppsala County were reviewed a second time six months later (Test-Retest Reliability). The patients were divided into those of < 70 years of age and those of ≥ 70 years of age, and the primary treatment strategy was recorded. Population data were retrieved from Statistics Sweden.

Statistics

The descriptive statistics and the specific annual incidence and treatment strategies of fractures were calculated for each age and sex subgroup. Mean values were presented with mean ± standard deviation. The trends were analysed with linear regression and presented with a correlation coefficient. The effects of age group and sex on treatment allocation and C2 fracture distribution were tested with the Chi-squared test (χ²). A value of p < 0.05 was considered as statistically significant.

The statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Statistics 22.0, IBM Corp., Armonk, NY).
Study III - Epidemiology of C2 Fractures in the 21st Century: A National Registry Cohort Study of 6,370 Patients from 1997 to 2014

All patients registered with the main or secondary diagnosis of C2 fracture (ICD-10: S12.1), and treated between 1 January 1997 and 31 December 2014, were extracted from the Swedish National Patient Registry (NPR). Also extracted were the treatment codes, which have been used to classify surgical procedures in Sweden since 1997. Hospitalization time is also available in the registry. Population registry data were abstracted from Statistics Sweden. ICD-10 has been validated for orthopaedic diagnosis with an accuracy of 95% for both main and secondary diagnoses until the third position. The specificity of the ICD-10 code S12.1 was validated in a dataset of 172 patients with ICD-10 S12.1 fractures from 2002 to 2014, where 0% false positive cases were found.

A subgroup analysis was performed for non-geriatric (20-69 years of age) and geriatric patients (70-99 years of age), as well as for non-surgical and surgical treatment. Patients receiving surgical treatment were identified using the Swedish surgical procedure codes for spinal fusion (“NAG”) and spinal fracture treatment (“NAJ”). Non-surgically treated cases whose treatment modality changed to surgery were registered as surgical patients. Patients younger than 20 and older than 99 years of age at the date of fracture were excluded. An inclusion flow diagram was prepared according to CONSORT statements (Moher, Hopewell et al. 2010).

Statistics

The mean values were presented ± standard deviation if not indicated otherwise.

Groups were tested for normal distribution with the Kolmogorov-Smirnov test. The groups were compared using the t-test for normally distributed variables; otherwise, the Wilcoxon test was applied. Trends were analysed with linear regression and presented with a correlation coefficient. The group proportions were tested with the Chi-squared test ($\chi^2$); $p < 0.05$ was regarded as statistically significant.

The differences in the age distribution of patients with C2 fractures treated with and without surgery were visualized with a density distribution plot. A logistic regression analysis identified covariates relevant for the assignment of surgical treatment, and was presented with a 95% confidence interval (CI) and statistical probability $p$. The literature review determined that age (Woods, Hohl et al. 2014), sex (Fehlings, Arun et al. 2013), the Charlson Comorbidity Index (CCI) (Ryang, Torok et al. 2016) and spinal cord injury (SCI)
(Konieczny, Gstrein et al. 2012) were relevant covariates in a model for surgical treatment assignment. Before removing those cases with patients under 20 and over 100 years of age from the dataset, a histogram of the age-related frequency of C2 fractures was prepared.

The statistical analysis was performed using the R commander (Version 3.3.0, R Foundation for Statistical Computing, Vienna, Austria).
Study IV- Surgical treatment improves the survival of elderly patients with an axis fracture – a national population-based multi-registry cohort study

All patients with the primary diagnosis of C2 fracture (ICD-10: S12.1), and treated between 1 January 1997 and 31 December 2014, were extracted from the NPR and merged with the Swedish Cause of Death Registry (CDR) for incident deaths. In the Swedish CDR, all deaths in Sweden are registered with the date and cause of death. While the date of death coverage is complete, the cause of death agrees only in 46% with the final hospital diagnosis (Johansson and Westerling 2000). Also registered were the main diagnosis and comorbidity, as well as the duration of hospitalization. Patients receiving surgical treatment were identified using the Swedish surgical procedure codes for spinal fusion (“NAG”) and spinal osteosynthesis (“NAJ”). The cohort was also divided into two groups depending on whether they were receiving non-surgical or surgical treatment.

Multiple admissions (cases with the same identification number but more than 12 months between admissions) and duplicate entries (cases with the same identification number) were removed from the dataset once valuable comorbidity data from the duplicate entries had been stored in the original record. Duplicate entries originated from separate recordings taken in each hospital if the patient had been referred to a specialized hospital. Furthermore, primarily non-surgically treated cases whose treatment modality changed to surgery within 12 months were registered as surgical patients. Patients of < 70 years of age and multiply traumatized patients (ICD-10: T07) were excluded from the study. The registered hospitalization duration for these patients was the combined non-surgical and surgical in-hospital treatment period.

From each record in the NPR, CCI was calculated using a previously validated algorithm based on ICD-10 codes. (Charlson, Szatrowski et al. 1994), (Sundararajan, Henderson et al. 2004)

Statistics

The mean values were presented ± the standard deviation. The groups were compared using the t-test for normally distributed variables; otherwise, the Wilcoxon test was applied. A probability of $p < 0.05$ was regarded as statistically significant. Logistic regression analysis, which identified the relevant covariates for the assignment of surgical treatment, Odds Ratio (OR) presented with 95% CI and statistical probability $p$ (Bagley, White et al. 2001). The Kaplan-Meier method was used to determine the mean and median survival rates for non-surgical and surgical treatment. The absolute survival rates among the non-surgical and surgical treatment groups and the relative risk reduction (RRR) at three months, one year and two years was determined,
while the survival curve was visualized using a Kaplan-Meier plot with 99% CI. The G-rho test was applied to test differences between the survival curves. The G-rho test examines whether or not there is a difference between two or more survival curves (Xu and Harrington 2001).

The proportional survival differences were tested depending on the treatment type using the Chi-squared test ($\chi^2$). Using the Cox proportional hazards regression method, multiple covariates that contributed to survival were entered, with the hazard ratio (HR) showing a 95% CI and probability $p$. Besides surgical treatment age, sex (Kim, Lee et al. 2008), spinal cord injury (Lidal, Snekkevik et al. 2007, Bajada, Ved et al. 2017) and CCI (Chikuda, Yasunaga et al. 2013) were identified as relevant covariates for survival. Since it was assumed that medical advancement had improved patient survival in general in recent decades, every year of admission was included as a covariate in the model. Covariates were treated as categorical variables and were entered or excluded in a stepwise fashion. The adjusted HR for a certain age and above was plotted over the age range with a 95% CI in order to identify a cut-off age where a particular treatment modality was no longer associated with a greater survival rate.

All statistical calculations were programmed in R (Version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria)
Study V - Protocol for a multicentre randomized controlled trial on displaced odontoid fractures type 2 in patients aged ≥ 75 years: The Uppsala Study on Odontoid Fracture Treatment (USOFT)

The USOFT is a multicentre, open-label, randomized controlled superiority trial evaluating the clinical superiority of the surgical treatment of odontoid fractures type 2. The primary endpoint at one year is the Neck Disability Index (NDI) score. The secondary endpoints are: Euroqol (EQ-5D), Activity of Daily Living (ADL), bone union, upper cervical stability and mortality. The study is not blinded. The USOFT is being conducted in three departments of orthopaedic surgery in three university hospitals (Uppsala University Hospital, Malmö University Hospital and Karolinska University Hospital Stockholm). This protocol follows the SPIRIT and CONSORT statements for clinical trial reporting (Chan, Tetzlaff et al. 2013, Boutron, Altman et al. 2017).

Included in this study are patients of ≥ 75 years of age with acute displaced odontoid fractures type 2 (Anderson and D'Alonzo 1974). Displacement is measured on a cervical spine CT scan and is defined as a 5-mm anterior transatorial displacement, any posterior translatory displacement or 10° of angulation (Greene, Dickman et al. 1997, Koivikko, Kiuru et al. 2004, Grauer, Shafi et al. 2005, Osman, Alageli et al. 2017). Excluded are patients with an American Society of Anaesthesiologists (ASA) score of ≥ 4, those in nursing care with dementia or those with anatomical cervical anomalies. The schedule for enrolment and intervention is shown in the CONSORT diagram (Figure 11), while the USOFT participant timeline is described in Table 2.

Allocation was randomized using the sequentially numbered, opaque sealed envelope (SNOSE) technique (Torgerson and Roberts 1999). The nonsurgical group is fitted with a rigid cervical collar for 12 weeks. The surgical group is treated with a posterior instrumented atlantoaxial (C1-C2) fusion and no postoperative collar. All participants are followed up with NDI, EQ-5D, socio-demographic and CT data at the time of injury, as well as six weeks, three months and 12 months post-treatment. At 12 months, a CT and a dynamic radiographic investigation of upper cervical stability is performed.
Figure 11. Consort flow diagram with the schedule for enrolment and intervention in USOFT.
Table 2: Participants timeline.

<table>
<thead>
<tr>
<th>Study period</th>
<th>Enrolment</th>
<th>Intervention</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time point</td>
<td>day 0</td>
<td>day 1</td>
<td>week 2</td>
</tr>
<tr>
<td>Elgibility assessment</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT scan</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Informed consent</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocation 1.surgery/2.non-surgery</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood samples</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCI</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ5D</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>NDI</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Katz ADL</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Socio-demographic data</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>DXA</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexion, extension radiograph</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sample size

Up to 50 participants will be included in the study, based on the following calculation of sample size: The minimal clinically important difference (MCID) of the NDI is 3.5 points (7%). Thus, 16 participants are needed in each group to reach 80% power with a two-sided significance level of $p < 0.05$ in a (clinically important) superiority study design. Adjusting for one-year mortality of 29% among those aged $\geq 70$ years treated non-surgically for axis fractures (unpublished data), eight additional participants must be recruited into each group. A minimum of 24 subjects must be included in each group.
Statistics

The baseline features of the patients will be described with descriptive statistics, using absolute numbers \((n)\) and percentages for categorical variables and the minimum, maximum, mean, SD and quartiles for quantitative variables. The number of patients who cross over to surgical treatment or drop out of follow-up will be documented. An intention to treat (ITT) analysis will be performed.

A multiple regression analysis of subgroup factors will allow for the determination of important factors affecting the NDI score. HRQoL will be evaluated with the EQ-5D by comparing the results from the two groups, using the independent t-test, the Mann-Whitney U test or Fisher’s exact test. A Chi-squared test \((\chi^2)\) will be used to compare the rate of non-union between the two groups. The VAS will be evaluated using the t-test, the Mann-Whitney U test or Fisher’s exact test. The Kaplan-Meier method will be used to determine the mean survival rate of non-surgical and surgical treatment after one year. Proportional survival differences according to treatment type will be tested with the Chi-squared test \((\chi^2)\). The covariates that contribute to survival will be entered in univariate and multivariate models using the Cox proportional hazards regression method, and the hazard ratio will be presented with a 95% CI. We will perform a separate analysis of participant sex (male or female), the specific type of surgery (categorical: Magerl-Atlas claw or Goel-Harms technique) and age decade at time of treatment (categorical: septuagenarian, octogenarian or nonagenarian). A value of \(p < 0.05\) will be considered as statistically significant.

For the statistical analysis, the R commander will be used (Version 3.3.0, R Foundation for Statistical Computing, Vienna, Austria). The statistical analysis will conform to the CONSORT statement for non-pharmacological interventions. Details of the statistical analysis are listed in Table 3.
<table>
<thead>
<tr>
<th>Variable/Outcomes</th>
<th>Hypothesis</th>
<th>Outcome measures</th>
<th>Methods of analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline data:</strong></td>
<td>There is no difference between the two groups</td>
<td>Gender, age, Katz ADL, CCI, nursing</td>
<td>Absolute numbers, Percentage percentages for categorical variables and the minimum, maximum, mean, SD and quartiles for quantitative variables.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>home/hospitalisation, smoking</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>There is a clinically important difference between the two groups</td>
<td>NDI (0%-100%) [continuous]</td>
<td>Students t-test, chi-square, Mann-Whitney, Fisher exact test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health-related Quality of Life</td>
<td>There is a clinically important difference between the two groups</td>
<td>EQ-5D [continuous]</td>
<td>Students t-test, chi-square, Mann-Whitney, Fisher exact test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>There is a clinically important difference between the two groups</td>
<td>VAS (0-100) [continuous]</td>
<td>Students t-test, chi-square, Mann-Whitney, Fisher exact test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-union</td>
<td>The non-union rate is lower in the surgical group</td>
<td>Bone bridge in CT [binary], mobility on extension-flexion radiographs [binary]</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>Mortality</td>
<td>The survival is greater in the surgical group</td>
<td>all-cause mortality [binary], time to death [continuous, censored]</td>
<td>Kaplan-Meier analysis, Cox regression models</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>There is no difference between the two groups</td>
<td>The bone density is &gt;2.5 standard deviations below normal DXA T-score [binary]</td>
<td>Students t-test, chi-square, Mann-Whitney, Fisher exact test</td>
</tr>
<tr>
<td><strong>Subgroup analysis:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>septuagenarians vs.</td>
<td>Treatment effect is diminished in nonagenarians</td>
<td></td>
<td></td>
</tr>
<tr>
<td>octogenarians vs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonagenarians</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goel-Harms technique vs.</td>
<td>There is no difference between the two groups</td>
<td></td>
<td></td>
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<tr>
<td>Magerl-technique</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs. Female</td>
<td>There is no difference between the two groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sensitivity Analysis:</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Per protocol analysis</td>
<td></td>
<td>all outcomes</td>
<td>Students t-test, chi-square, Mann-Whitney, Fisher exact test</td>
</tr>
<tr>
<td>Adjusting for baseline</td>
<td>all outcomes</td>
<td>Uni-and multivariate adjusted logistic regression and Cox proportional hazard models</td>
<td></td>
</tr>
<tr>
<td>covariates</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ethics

In the thesis, Study 1 was a systematic review and did not involve patients; no handling of sensitive patient data was necessary.

Regarding Studies 3 and 4, registry-based research sometimes handles sensitive patient data. If the data are not anonymized, they could be connected to an individual and violate the individual’s privacy. Therefore, prior to transmitting the data, the Swedish National Board of Health and Welfare anonymized the individual personal identification numbers using a key that remained with the agency. We were provided with a predefined extract from the national registries by the Swedish National Board of Health and Welfare (specification number: 13062/2015).

Studies 2 to 4 were approved by the Regional Ethics Committee of Uppsala (dnr 2010/131/1). Study 4 was registered with ClinicalTrials.gov, NCT 02839057. Study 5 was approved by the Regional Ethics Committee of Uppsala (dnr 2011/068) and registered with ClinicalTrials.gov, NCT02789774.
Results and discussion

Study I

Results and discussion

Thirty-eight publications met the inclusion criteria out of 608 citations. The inclusion flow is illustrated in Figure 12. All of the studies except one were retrospective studies (Vaccaro, Kepler et al. 2013). The included articles are presented in Table 4.

Only one study met the criteria for a “moderate” level of evidence (the AOSpine GOF study) (Fehlings, Arun et al. 2013, Smith, Kepler et al. 2013, Vaccaro, Kepler et al. 2013); the rest of the studies were “low” or “very low” in terms of evidence quality.

Citations found
- PubMed MEDLINE (n= 608)
- Ovid MEDLINE (n=80)
- ISI Web of Knowledge (n=161)

Title/Abstract exclusion (n=761)

Retrieved for full-text evaluation (n=88)

Excluded at full-text review (50)

Publications included (38)

*Figure 12: Flow chart from the literature research. MeSH terms: “odontoid AND fracture AND elderly”.*
Table 4: Included articles.

<table>
<thead>
<tr>
<th>Author</th>
<th>N elderly</th>
<th>Non-surgical treatment</th>
<th>Surgical treatment</th>
<th>Minimum follow-up</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td>N collar</td>
<td>N cast</td>
<td>N halo</td>
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<td>Pepin, J. W., et al. (1985)</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td></td>
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<tr>
<td>Dunn and Sejjeskog (1986)</td>
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<td></td>
<td>9</td>
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</tr>
<tr>
<td>Lind, B., et al. (1987)</td>
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<td>2</td>
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<tr>
<td>Montesano, P. X., et al. (1991)</td>
<td>6</td>
<td></td>
<td>6</td>
<td></td>
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<tr>
<td>Jeanneret and Magerl (1992)</td>
<td>2</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hanigan, W. C., et al. (1993)</td>
<td>16</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ryan, M. D. and T. K. Taylor (1993)</td>
<td>14</td>
<td>4</td>
<td>9</td>
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<tr>
<td>Paini, R. S., et al. (1996)</td>
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<td>16</td>
<td></td>
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<tr>
<td>Berlemann, U. et al. (1997)</td>
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<tr>
<td>Seybold, E. A. and J. C. Bayley (1998)</td>
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<td>3</td>
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<td>Kuntz, C. E. et al. (2000)</td>
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<td>3</td>
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<td>Andersson, S., et al. (2000)</td>
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<td>1</td>
<td>10</td>
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<tr>
<td>Ziai, W. C. and R. J. Hurtbert (2000)</td>
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<td>Borm et al. (2003)</td>
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<td>Cornedford, M., et al. (2003)</td>
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<td>Frangen, T. M., et al. (2007)</td>
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<td>Plater, P., et al. (2007).</td>
<td>41</td>
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<tr>
<td>Smith, H. E., et al. (2008)</td>
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<td>24</td>
<td>16</td>
<td>10</td>
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<tr>
<td>Koehl, F., et al. (2008)</td>
<td>42</td>
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<td>32</td>
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<tr>
<td>Stulik, J., et al. (2008)</td>
<td>20</td>
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<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Omeis, J., et al. (2009)</td>
<td>29</td>
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<td>16</td>
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<tr>
<td>Faggin et al. (2010)</td>
<td>108</td>
<td>64</td>
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<td>Butler, J. S., et al. (2010)</td>
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<td>14</td>
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<td>Dailey, A. T., et al. (2010)</td>
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<tr>
<td>Hou, Y., et al. (2011)</td>
<td>43</td>
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<tr>
<td>Osti, M., et al. (2011)</td>
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<tr>
<td>Schoenfeld, A. J., et al. (2011)</td>
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<td>84</td>
<td>28</td>
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</tr>
<tr>
<td>Mayer et al. (2011)</td>
<td>18</td>
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<td></td>
<td></td>
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<tr>
<td>Hénaux et al. (2011)</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chapman, J., et al. (2013)</td>
<td>157</td>
<td></td>
<td>(non-surgical)</td>
<td></td>
</tr>
<tr>
<td>Fehlings et al. (2013)</td>
<td>322</td>
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<tr>
<td>Smith et al. (2013)</td>
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<tr>
<td>Vaccaro et al. (2013)</td>
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<tr>
<td>Kohlhof, H., et al. (2013)</td>
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<td>Molinari, R. W., et al. (2013)</td>
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<td>26</td>
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<tr>
<td>Stetzljen, C., et al. (2013)</td>
<td>9</td>
<td></td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>
Does surgery improve survival in elderly patients with a type 2 odontoid fracture?

Twenty-nine publications included mortality data from 1,284 patients. The Kaplan–Meier curve shows a difference between non-surgically and surgically treated patients with an odontoid fracture type 2 (Figure 13). Many studies ended their investigation after 24 months, which due to right-sided censoring led to a major drop in the Kaplan-Meier survival curve; but there was also a drop in the survival curve at three months and 12 months post-treatment. The reason for these drops is interpreted not as being drop in survival at these times, but as the time at which these patients had a follow-up. The Kaplan-Meier curve aimed to show the effect of different treatment modalities on survival. Non-surgical treatment was associated with higher mortality than surgical treatment up to three years after the accident. A younger age and surgical treatment were associated with improved survival (Cox regression: surgical treatment HR 0.64, \( p < 0.001 \), patient age HR 1.22, \( p < 0.001 \)).

![Kaplan-Meier survival curve](image)

*Figure 13: Kaplan-Meier survival curve for the included cases with surgically and non-surgically treated odontoid fractures type 2 (n=1,284)*
The largest retrospective cohort published so far on odontoid fractures in the elderly population is the AOSpine North America Geriatric Odontoid Fracture Mortality Study, which included 322 patients (Chapman, Smith et al. 2013). After adjusting for the effects of patient age, sex and comorbidities, surgically treated patients \( n = 165 \) had a significantly better 30-day survival rate than non-surgically treated patients \( n = 157 \) (HR = 3.0; 95% CI: 1.51–5.94; \( p = 0.0017 \)); this effect prevailed until the final follow-up (HR = 1.35; 95% CI: 0.97–1.89; \( p = 0.079 \)). Schoenfeld et al. (Schoenfeld, Bono et al. 2011) found in their retrospective cohort of 156 patients an increased three month and one year mortality rate in the non-surgical group, although this did not reach statistical significance (both \( p = 0.06 \)). The authors subdivided their cohort into three age groups. An improved survival rate with surgical treatment was most impressive in the group aged between 65 and 74 years (HR = 0.4; 95% CI: 0.1–1.5) and lesser in the group aged between 75 and 84 years (HR = 0.8; 95% CI: 0.3–2.3). It is possible that patients above the age of 85 actually have a greater mortality rate if treated surgically (HR = 1.9; 95% CI: 0.6–6.1).

According to the above, surgical treatment seems to be favourable over non-surgical treatment in patients between 65 and 85 years of age in terms of survival. There could be a selection bias when treating patients with more severe co-morbidity non-surgically, even though in the North American AO Spine study, they could not find any baseline differences between the two groups (Vaccaro, Kepler et al. 2013). There was conflicting evidence that, over 85 years of age, patients possibly had a greater risk of mortality if treated surgically (quality of evidence: very low).


**Which stabilization method has the best fracture healing?**

Data on the fusion rate and surgical treatment of 669 patients (from 29 publications) were available. Treatment with a collar or halo-vest had non-union rates of 39% and 41%, respectively. Posterior fusion was superior to anterior fusion in the success of bone union (11% vs 27% non-union) (Table 5). Most studies from the 1980s and 1990s focused on radiographic healing; therefore, this aspect is well documented. On the other hand, there could have been an underreporting of the rate of bone non-union, as the use of CT was rare in the evaluation of healing. Bone union in odontoid fractures type 2 was superior when treated by posterior fusion than anterior fixation, which was superior to collar treatment, which was finally superior to halo-vest treatment (quality of evidence: low).
Table 5: Treatment allocation and non-union rate for 669 cases.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Non-union</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collar</td>
<td>154</td>
<td>60</td>
<td>39%</td>
</tr>
<tr>
<td>Halo</td>
<td>73</td>
<td>30</td>
<td>41%</td>
</tr>
<tr>
<td>Anterior</td>
<td>293</td>
<td>79</td>
<td>27%</td>
</tr>
<tr>
<td>Posterior</td>
<td>149</td>
<td>17</td>
<td>11%</td>
</tr>
<tr>
<td>Total</td>
<td>669</td>
<td>186</td>
<td>28%</td>
</tr>
</tbody>
</table>

Is the clinical outcome worse in non-union odontoid fractures?
Two studies addressed the clinical outcome using NDI score; they found no differences in NDI in non-union or radiographic healing (Molinari, Dahl et al. 2013, Smith, Kepler et al. 2013).

Odontoid non-union in the elderly population was not associated with a worse clinical outcome. Still, the good results of revision surgery in cervical non-union suggest that there are at least some biomechanical components in persistent postoperative pain following anterior cervical fusion (Raizman, O'Brien et al. 2009).

There have also been some reports of delayed myelopathy in elderly patients with odontoid fractures. Crockard et al. found that myelopathy often occurs several years after the initial trauma (Crockard, Heilman et al. 1993) (quality of evidence: low).

Is surgical treatment associated with more complications compared to non-surgical treatment in odontoid fractures type 2?
Only one study, the AOSpine North American GOF, fulfilled the criteria for a prospective study design, which is needed to estimate the complication rate (Vaccaro, Kepler et al. 2013). They found a non-significant difference ($p = 0.48$) in the complication rate between non-surgically and surgically treated patients. Surgically treated patients were more likely to suffer from dysphagia (no subgroup analysis was performed, so it is unclear as to whether the surgery was an anterior screw fixation or posterior fusion).

No treatment modality was superior to any other regarding complications (quality of evidence: low).
Conclusion

The following conclusions have been drawn from this systematic review:

1. Surgical treatment of odontoid fractures type 2 improves the survival rate of patients aged between 65 and 85 years compared to non-surgical treatment.
   (Quality of evidence: moderate)

2. Primary posterior fusion for odontoid fractures type 2 in the elderly results in the highest bone union rate.
   (Quality of evidence: low)

3. Odontoid non-union is not associated with worse clinical or functional results in the elderly population.
   (Quality of evidence: low)

4. The complication rate of non-surgical treatment is similar to the complication rate of surgical treatment of odontoid fractures type 2 in the elderly population.
   (Quality of evidence: low)
Study II

Results and discussion

Fracture classification and distribution

Two hundred and thirty-three patients (118 women), with a mean age of 72 ± 19 years of age (range: 17–97), were treated for a C2 fracture between January 2002 and December 2014 in Uppsala County and Malmö City.

Seventy patients (20 women), with a mean age of 48 ± 15 years, were <70 years of age. The distribution of C2 fractures among the patients aged <70 years consisted of 38 odontoids, 17 Hangman’s and 15 atypical fractures. In the group aged ≥ 70 years, 145 of the fractures were odontoid, nine were Hangman’s and nine were atypical (Table 6). Eighty-nine percent of the older age group (≥ 70 years of age) had suffered from odontoid fractures type 2 or 3 (Figure 14). The intraobserver reliability was 82% on the primarily diagnosed odontoid fracture type 2 or 3 (unpublished data).


<table>
<thead>
<tr>
<th>Age</th>
<th>Total (n)</th>
<th>Fracture Class (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>O1</td>
</tr>
<tr>
<td>&lt;70</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>≥70</td>
<td>163</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>233</td>
<td>2</td>
</tr>
</tbody>
</table>
There was a statistical difference in terms of sex; in the younger age group of < 70 years of age, C2 fractures were more common in men, while in patients of > 70 years of age, women were more likely to suffer from C2 fractures. The proportion of patients with odontoid fractures type 2 increased with age. The distribution is similar to previously published data (Anderson and D’Alonzo 1974, Greene, Dickman et al. 1997, Grauer, Shafi et al. 2005) (Table 7). There were only 26 cases of Hangman’s fracture in our study; they were evenly distributed, with 54% type 1 and 46% type 2 fractures. These figures are exactly the same as previously published data (Al-Mahfoudh, Beagrie et al. 2016) (Table 8). 10% of all C2 fractures were atypical in our study; 21% occurred in the population aged < 70 years, while 6% of them occurred in patients aged ≥ 70 years. One explanation for why atypical fractures are more common in the younger population (< 70 years of age) could be that they comprise a variety of fracture patterns and result from high-energy injuries, which are more common in the younger population.

**Incidence**

The incidence of C2 fractures was 3.8 per 100,000 people between the years 2002 and 2014. The mean incidence from 2002 to 2014 is presented in Table 9.

In the age group of ≥ 70 years, the annual incidences of odontoid fractures type 2 and 3 together almost tripled from 7.4 per 100,000 people in the year 2002 to 22.1 per 100,000 people in the year 2014 (Figure 15). No correlation was found in the other C2 fracture subgroups.
Table 7: Earlier publications on distribution of odontoid fractures. Present study in grey.

<table>
<thead>
<tr>
<th>Author</th>
<th>Anderson and D’Alonzo</th>
<th>Dunn et al.</th>
<th>Hanssen et al.</th>
<th>Fuji et al.</th>
<th>Greene et al.</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>49</td>
<td>110</td>
<td>42</td>
<td>52</td>
<td>199</td>
<td>183</td>
</tr>
<tr>
<td>Age(mean)</td>
<td>41</td>
<td>*</td>
<td>50</td>
<td>34</td>
<td>41</td>
<td>76</td>
</tr>
<tr>
<td>Type 1</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
<td>4%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Type 2</td>
<td>65%</td>
<td>80%</td>
<td>62%</td>
<td>60%</td>
<td>60%</td>
<td>69%</td>
</tr>
<tr>
<td>Type 3</td>
<td>31%</td>
<td>20%</td>
<td>38%</td>
<td>36%</td>
<td>39%</td>
<td>30%</td>
</tr>
</tbody>
</table>

*missing value

Table 8: Earlier publications on Hangman's fractures. Present study in grey.

<table>
<thead>
<tr>
<th>Author</th>
<th>Effendi et al.</th>
<th>Levine et al.</th>
<th>Greene et al.</th>
<th>Ferro et al.</th>
<th>Rafid Al-Mahfoudh et al.</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>131</td>
<td>52</td>
<td>74</td>
<td>16</td>
<td>41</td>
<td>26</td>
</tr>
<tr>
<td>Age(mean)</td>
<td>31</td>
<td>35</td>
<td>41</td>
<td>39</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Type 1</td>
<td>65%</td>
<td>29%</td>
<td>72%</td>
<td>31%</td>
<td>54%</td>
<td>54%</td>
</tr>
<tr>
<td>Type 2</td>
<td>28%</td>
<td>61%</td>
<td>27%</td>
<td>69%</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td>Type 3</td>
<td>7%</td>
<td>10%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Table 9: Mean annual incidence of C2 fractures.

<table>
<thead>
<tr>
<th>Age and gender</th>
<th>Mean population-at-risk</th>
<th>Mean annual incidence (per 100000 inhabitants) 2002-2014</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Odontoid fractures</td>
</tr>
<tr>
<td>Men &lt;70</td>
<td>201402</td>
<td>1.0</td>
</tr>
<tr>
<td>Women &lt;70</td>
<td>201444</td>
<td>0.5</td>
</tr>
<tr>
<td>Men ≥70</td>
<td>28713</td>
<td>15.8</td>
</tr>
<tr>
<td>Women ≥70</td>
<td>41382</td>
<td>16.0</td>
</tr>
<tr>
<td>Total</td>
<td>472941</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Figure 15: Annual incidence of odontoid fractures in patients ≥70 years of age 2002-2014.
The increased incidence of odontoid fractures type 2 and 3 could be explained not only by improved diagnostics using computed tomography (CT), but also the active lifestyle of the elderly in combination with decreased institutionalization (Bravell, Berg et al. 2009). Even the relative increase of type 3 odontoid fractures could be explained by the increasing differentiation possibilities offered by CT. In this study, the Grauer classification was used, which could lead to a lower estimate of odontoid fractures type 2 compared to odontoid fractures type 3 (Grauer, Shafi et al. 2005). One explanation for the increased incidence of odontoid fractures type 2 and 3 could be improved diagnostic capabilities.

**Treatment**

Forty percent of C2 fractures were treated surgically. Fifty-three percent of odontoid fractures type 2, 19% of type 3 odontoid fractures, 100% of Hangman’s fractures type 2 and 14% of Hangman’s fractures type 1 were treated surgically. On the other hand, only 8% of atypical fractures were treated surgically (Table 10). Regarding assignment to surgical treatment, there was no statistical difference between the < 70 years age group and the ≥ 70 years one ($p = 0.57$), or between sexes ($p = 0.55$).

From 2002 to 2014, the proportion of patients with odontoid fractures type 2 who were treated surgically increased, both in the younger and older age group ($r = 0.70$, $p < 0.01$) (Figure 16). This could not be seen in the other fracture sub-classifications.

In the US, there has been a trend towards surgical treatment for elderly patients suffering from an odontoid fracture type 2 (Nourbakhsh, Shi et al. 2009, Smith, Kerr et al. 2010). In this study, a trend towards surgical management was also found. It is doubtful as to whether this result could be generalized to the rest of Sweden.

**Table 10: Age-, and gender treatment allocation of C2 fractures.**

<table>
<thead>
<tr>
<th>Age and gender</th>
<th>C2 fractures Total (n)</th>
<th>Treatment (surgery/total number)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O1</td>
<td>O2</td>
</tr>
<tr>
<td>Men &lt;70</td>
<td>50</td>
<td>0/0</td>
</tr>
<tr>
<td>Women &lt;70</td>
<td>20</td>
<td>0/2</td>
</tr>
<tr>
<td>Men ≥70</td>
<td>65</td>
<td>0/0</td>
</tr>
<tr>
<td>Women ≥70</td>
<td>98</td>
<td>0/0</td>
</tr>
<tr>
<td>Total</td>
<td>233</td>
<td>0/2</td>
</tr>
</tbody>
</table>
Figure 16: Treatment trend of odontoid fracture type 2, 2002-2014.
For odontoid fractures type 3, the recommended treatment is non-surgical with a collar (Huybregts, Jacobs et al. 2013, Patel, Zakaria et al. 2015), which is consistent with the results from our study.

Hangman’s fractures type 1 are most often treated non-surgically, while types 2 and 3 are treated surgically, depending on degree of displacement (Li, Dai et al. 2006, Ferro, Borgo et al. 2012). In our study, all Hangman’s type 2 fractures were treated surgically, as well as even some of the Hangman’s fractures type 1.

Atypical fractures comprised a variety of fracture patterns, and no recommendations are available. In our study, the predominant treatment was non-surgical.

**Conclusion**

This study has validated the previously published distribution of C2 fracture subgroups, and has presented new values for subgroup proportions for two regions in Sweden. These values allow for further population-based research in which subgroup proportions have to be estimated from ICD-10 codes. Eighty-nine percent of C2 fractures in the elderly population are odontoid fractures type 2 or 3. An increased incidence of odontoid fractures type 2 and 3 has been observed among the elderly. The proportion of surgically treated odontoid fractures type 2 has increased over the last two decades in Uppsala County and Malmö City. National population-based studies could improve the current evidence available and strengthen treatment guidelines.
Study III

Results and discussion

This study presents reliable data from a large dataset on the increased incidence and treatment trends of C2 fractures in Sweden.

Six thousand three hundred and seventy patients with the primary and secondary diagnosis of fracture of the second vertebrae (S12.1) were included in the study. The mean age was 72 ± 18 years. Fifty-one percent were male. The group was divided into non-geriatric patients of < 70 years of age (n = 2,256) and geriatric patients of ≥70 years of age (n = 4,114).

The inclusion flow chart is shown in Figure 17.

Figure 17: Inclusion flow chart of C2 fracture.
Baseline data are shown in Table 11. The Charlson Comorbidity Index (CCI) was 4.9 ± 2.5 and spinal cord injury (SCI) was present in 2% (n = 140). 10% (n = 630) had a concomitant C1 fracture.

Table 11: Baseline data. CCI: Charlson comorbidity index, SCI: spinal cord injury, T: thoracic fracture, L: lumbar fracture.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>age</th>
<th>sex</th>
<th>N CCI</th>
<th>N SCI</th>
<th>spinal fracture</th>
<th>surgical technique</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>surgical</td>
<td>1681</td>
<td>68±17</td>
<td>1013</td>
<td>668</td>
<td>4.4±2.3</td>
<td>77</td>
<td>236</td>
</tr>
<tr>
<td>non-surgical</td>
<td>4689</td>
<td>73±18</td>
<td>2277</td>
<td>2412</td>
<td>5.1±2.6</td>
<td>63</td>
<td>394</td>
</tr>
<tr>
<td>all</td>
<td>6370</td>
<td>72±18</td>
<td>3290</td>
<td>3080</td>
<td>4.9±2.5</td>
<td>140</td>
<td>630</td>
</tr>
</tbody>
</table>

Incidence

The incidence of C2 fractures doubled in the period 1997 to 2014 from three to six/100,000 inhabitants (p < 0.01). The incidence of C2 fractures in the geriatric group increased from 10.2 to 23.7 per 100,000 people from 1997 to 2014; this could not be seen in the non-geriatric subgroup (Figure 18).

Figure 18: C2 fracture incidence from 1997 to 2014
A bimodal distribution was found with a peak in those aged between 20 and 25, as well as in those aged between 80-85 years (Figure 19).

**Figure 19: Distribution of C2 fractures reveals a bimodal frequency.**

As the ICD-10 code does not allow for the differentiation of C2 fractures, these results must be interpreted with caution. In an earlier study, we presented that 89% of C2 fractures in patients of $\geq 70$ years of age were odontoid fractures type 2 and 3. We also found that there was not an increased incidence in any other subgroup other than odontoid fractures type 2 and 3 between 2002 and 2014 (Robinson, Moller et al. 2017). It is assumed that odontoid fractures type 2 and 3 have also led to the increased incidence of fractures in the elderly population in this study.

One explanation for the increased incidence of C2 fractures is diagnostic bias; nowadays, we use computed tomography instead of conventional radiographs as the primary diagnostic instrument (Barker, Anderson et al. 2006). The number of falls among the elderly population is also substantial (Dionysiotis 2012), with a 78% incidence for those with four or more risk factors. These risk factors include, for instance, weakness, deteriorated reflexes, unsteady gait, confusion and some medications (Tinetti, Speechley et al. 1988, Rubenstein 2006). Five percent of these falls cause a fracture (Rubenstein 2006). The elderly now receive better treatment for comorbidities than they did in previous decades (Health Quality 2008). This has led to a higher level of activity among the elderly, along with a higher risk of falling; however, inactive individuals are also at high risk of falls (Dionyssiotis 2012). The orthostatic effects of medication, such as benzodiazepines and antihypertensive drugs, may also lead to falls. Furthermore, the fact that the healthcare system in Sweden encourages geriatric patients to live in their own homes instead of
in nursing homes affects the possibilities of supervision and accessibility, and is a plausible cause of domestic falls (Health Quality 2008, Bravell, Berg et al. 2009). Otherwise, patients at nursing homes are at higher risk of falls (Rubenstein 2006, Dionyssiotis 2012). The combination of falls, a stiff lower cervical spine and osteoporosis could explain the increased incidence of C2 fractures in the elderly population (Kaesmacher, Schweizer et al. 2017).

**Treatment**

Twenty-six percent of patients with a C2 fracture were treated surgically: 34% in the non-geriatric group and 22% in the geriatric group (χ²-test, \( p < 0.01 \)). Stratified for sexes (51% male, 49% female), 31% of male and 22% of female patients received surgical treatment (χ²-test, \( p < 0.01 \)). In a logistic regression model, the odds ratio of surgical treatment assignment was significantly greater for younger age groups, males, SCI and an earlier year of admission (Table 12).

*Table 12: Surgical treatment assignment presented with Odds Ratio (OR)*

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% C.I.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.5 %</td>
<td>97.5 %</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>0.99</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>1.42</td>
<td>1.26</td>
<td>1.59</td>
</tr>
<tr>
<td><strong>Spinal Cord Injury</strong></td>
<td>2.94</td>
<td>2.08</td>
<td>4.16</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Index</strong></td>
<td>0.96</td>
<td>0.92</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Year of admission</strong></td>
<td>0.96</td>
<td>0.94</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Surgical treatment with posterior fusion is more common in the elderly patients, when comparing anterior and posterior surgery (Figure 20). This difference does not reach significant difference. When interpreting these results, one has to consider that all the C2 fracture subtypes are included. A major part of the Hangman’s fractures is treated with anterior surgery, as well as the odontoid fractures type 2 in the younger population.

There was a linear trend in the geriatric group towards non-surgical treatment between 1997 and 2014 (\( r = -0.94, p < 0.05 \)) (Figure 21).
The trend towards non-surgical treatment in elderly patients stands in contrast to what we found in our earlier study, as well as to other recent published data (Chapman, Smith et al. 2013, Choma, Rechtine et al. 2015). This trend could not be seen in the younger population. This negative trend for surgery could be explained by the availability of high-level trauma care in university cities,
which is not available in rural parts of Sweden. The fear of overtreatment could be a factor contributing to the trend towards the non-surgical treatment of cervical fractures. Patient comorbidity could be another explanation for physicians’ tendency to use a cervical collar in the belief that this will avoid further damage. In contrast, recently published results suggest that the surgical stabilization of C2 fractures reduces morbidity and mortality in elderly patients with greater comorbidity (Majercik, Tashjian et al. 2005, Kaesmacher, Schweizer et al. 2017).

Conclusion
This study identified an increased incidence of C2 fractures over the last two decades, along with a decreased proportion of surgically treated elderly patients.
Study IV

Results and discussion

3,375 elderly patients were included (43% male), with a mean age of 83 ± 7 years. Twenty-two percent (n = 757) were treated surgically. The inclusion flow diagram is presented in Figure 22. 3.7% of patients with C2 fractures had a concomitant C1 fracture, and 3.7% had a subaxial cervical fracture. Acute spinal cord injury was present in 0.9% of all the included patients. The baseline data are summarized in Table 13.

![Inclusion flow diagram 1997-2014.](image)

**Table 13: Baseline data of the included patients ≥70 years with C2 fractures according to treatment. CCI: Charlson Comorbidity Index. SCI: Spinal Cord Injury.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N Subjects</th>
<th>age years</th>
<th>gender</th>
<th>hospitalisation days</th>
<th>comorbidity CCI</th>
<th>concomitant spinal injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-surgical</td>
<td>2618</td>
<td>83.4 ± 6.9</td>
<td>N male: 1073, N female: 1545</td>
<td>12 ±14</td>
<td>6.2 ± 1.7</td>
<td>73, 95, 16</td>
</tr>
<tr>
<td>surgical</td>
<td>757</td>
<td>79.9 ± 6.3</td>
<td>386, 371</td>
<td>16 ± 16</td>
<td>5.7 ± 1.6</td>
<td>52, 29, 15</td>
</tr>
<tr>
<td>all</td>
<td>3375</td>
<td>82.6 ± 6.9</td>
<td>1459, 1916</td>
<td>13 ± 15</td>
<td>6.1 ± 1.6</td>
<td>125, 124, 31</td>
</tr>
</tbody>
</table>
Treatment selection

Surgical treatment assignment was based on younger age (OR = 0.93, CI: 0.92-0.95, p < 0.001), male sex (OR = 1.28, CI: 1.07-1.53, p = 0.006) and earlier years of treatment (OR = 0.91, CI: 0.89-0.92, p < 0.001). There was no statistical significance for comorbidity in the choice of treatment (OR = 1.00, CI: 0.94-1.06, p = 0.99).

There was a strong linear trend towards less surgical treatment for patients with the main ICD-10 code S12.1 ‘fracture of the second vertebrae’ decreasing from 34% of patients surgically treated in 1997 to 11% in 2014 (r = -0.93, p < 0.001).

There has been a trend in Sweden towards the non-surgical treatment of C2 fractures in elderly patients of ≥ 70 years of age (page Robinson, Olerud et al. 2017), which stands in contrast to recent published studies. In a North American retrospective cohort, the treatment trend for odontoid fractures type 2 has been in favour of surgery over the last two decades (Smith, Vaccaro et al. 2008). In our recent cohort study on odontoid fracture treatment in two Swedish tertiary referral centres, we identified an increased trend towards surgical treatment (page 49). Clearly, regional differences exist in the interpretation of current treatment evidence (Vaccaro, Kepler et al. 2013).

Survival

The mean survival duration after a non-surgically treated C2 fracture was 4.6 years, while it was 6.1 years for surgically treated patients.

The one-year survival rate was 72% (n = 1,856) for non-surgically treated patients, and 81% (n = 614) for surgically treated patients (p < 0.001, RRR = 11%). In a Kaplan-Meier curve adjusted for age, sex, CCI, and year of treatment the difference in survival of non-surgically and surgically treated patients was visualized (Figure 23).

In a univariate analysis, non-surgically treated patients experienced a higher risk of dying during follow-up than surgically treated patients (HR = 1.37, 95% CI: 1.25-1.51). In a multivariate analysis adjusted for age (decades), sex (male or female), CCI (moderate, high or very high) and the decade of treatment, we again found the lowest mortality among surgically treated patients. The increased risk of mortality among non-surgically treated patients was reduced to some extent (HR = 1.14, 95% CI: 1.03-1.26) (Table 14). Surgical treatment, however, was not associated with improved survival above 88 years of age (95% CI: 85-92) (Figure 24).
Table 14: The results of univariate and multivariate Cox proportional hazards regression are presented with 95% C.I.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>N Deaths/Subjects</th>
<th>N Person-years</th>
<th>Univariate</th>
<th>Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>categories</td>
<td></td>
<td>HR (95%-C.I.)</td>
<td>p</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-surgical</td>
<td>1856/2618</td>
<td>10212</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>surgical</td>
<td>559/757</td>
<td>4178</td>
<td>0.73 (0.66-0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (decade)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79 years</td>
<td>657/1154</td>
<td>6744</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>80-89 years</td>
<td>1239/1627</td>
<td>6102</td>
<td>2.43 (2.20-2.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>90-99 years</td>
<td>510/585</td>
<td>1525</td>
<td>4.51 (3.99-5.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>100+ years</td>
<td>9/9</td>
<td>19</td>
<td>6.77 (3.50-13.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1345/1916</td>
<td>8423</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>Male</td>
<td>1070/1459</td>
<td>5967</td>
<td>1.14 (1.05-1.23)</td>
<td>0.002</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (4-5)</td>
<td>807/1364</td>
<td>8059</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>High (6-7)</td>
<td>1182/1517</td>
<td>5170</td>
<td>1.52 (1.41-1.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Very High (&gt;=8)</td>
<td>426/494</td>
<td>1161</td>
<td>2.85 (2.64-3.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Year of fracture (decade)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990s</td>
<td>334/349</td>
<td>2246</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>2000s</td>
<td>1441/1751</td>
<td>8778</td>
<td>1.13 (1.02-1.25)</td>
<td>0.016</td>
</tr>
<tr>
<td>2010s</td>
<td>640/1275</td>
<td>3366</td>
<td>0.98 (0.91-1.05)</td>
<td>0.531</td>
</tr>
</tbody>
</table>
Figure 23: Adjusted survival curve for 3,375 elderly patients with a C2 fracture. Adjusted for age, sex, CCI, and year of treatment.

Figure 24: HR of surgical treatment (blue line) with 95% C.I. (grey shaded area) according to patient age. Adjusted for sex, CCI, and year of treatment.
A meta-analysis of 1,284 retrospectively collected patients with odontoid fractures type 2 finds a one-year mortality rate of 23% for non-surgical treatment and 11% for surgical treatment \((p < 0.001)\) (page 41), similar results to those found in this study. A prospectively collected cohort of 159 patients of > 64 years of age with an odontoid fracture type 2 reports a one-year mortality rate of 26% among the non-surgically treated and 14% among the surgically treated \((p = 0.059)\) (Vaccaro, Kepler et al. 2013).

In this study, we found a one-year mortality rate of 28% among non-surgically treated patients and 19% among surgically treated patients. Probable causes of the decreased survival of the non-surgically treated group (halo-vest or cervical collar treatment) are the restriction of the upper thoracic mobility thus leading to impaired respiratory function (Majercik, Tashjian et al. 2005) and dysphagia, which may lead to aspiration and impairment of swallowing, leading to dehydration and malnutrition (Leibovitz, Baumoehl et al. 2007, Carrion, Cabre et al. 2015).

**Hospitalization**

Over the last two decades, the mean total duration of hospitalization for C2 fracture treatment has decreased from 16 days (median: 12 days, 95% CI: 12-20) to nine days (median: 11 days, 95% CI: 8-10) for non-surgically treated patients. For surgically treated patients, it decreased from 28 days (median: 21 days, 95% CI: 18-38) in 1997 \((p = 0.03)\) to 13 days (median: seven days, 95% CI: 10-16) in 2014 \((p < 0.001)\) \((r =-0.20)\).

Non-surgical treatment was associated with a four-day shorter mean hospitalization time.

One explanation for the prolonged hospitalization time for the surgically treated patients could be the preparation and optimization time necessary for surgical interventions. Also, the fact that the patient could have been treated non-surgically primarily, and then converted into surgery after a week, could add days to the hospitalization time.

**Conclusion**

This cohort study documents the benefit of surgery in consideration of short- and long-time survival rates. The relative risk reduction (RRR) one year after the injury was 11%. The age of 88 years was found to be a cut-off age after which surgery no longer had a positive effect on survival.
Study V

Results and Discussion

Patient inclusion in the USOFT started in February 2012 in the Department of Surgical Sciences at Uppsala University Hospital, Uppsala, Sweden, and in October 2014 in the Department of Spine Surgery at Malmö University Hospital, Malmö, Sweden. Recruitment is planned to be completed before 31 December 2018.

This is the first randomized controlled study on the treatment of odontoid type 2 fractures in the elderly population. The study primarily addresses NDI and HRQoL, which are important pillars of evidence-based care. Due to the frailty of the geriatric study participants, with a high mortality rate from different causes, we have discarded mortality as a primary endpoint as it would require a significantly greater sample size.

Several authors have found that the surgical treatment of odontoid fractures type 2 can minimize mortality and reduce pulmonary complications in elderly patients (Chen, Boakye et al. 2012). In Sweden, surgery reduces the one-year mortality rate of C2 fractures by 11% (page 59) Surgery is associated with a four day longer hospital stay; therefore, the results of the USOFT will have direct implications for medical decision-making.

Conclusion

The results of this study will provide the highest level of evidence regarding the treatment of odontoid fractures type 2 in the elderly population. The results should be applicable in clinical settings with the possibility of improving patient outcomes and safety in the fragile elderly population. The quality-adjusted life years gained through optimal treatment will support policy makers and clinicians in making informed decisions.
General discussion

The above presented studies had the following main findings: 1) 89% of C2 fractures are odontoid fractures type 2 or 3. 2) In Sweden there has been an increased incidence of C2 fractures in the elderly population. 3) There has a trend towards less surgical treatment for elderly patients. 4) In two level one trauma hospitals, the trend went in the opposite direction, towards more surgical treatment for elderly patients with a type 2 odontoid fracture. 5) The one-year survival relative risk reduction (RRR) is 11% when treated surgically, increasing to 19% after two years. 6) After 88 years of age, surgical treatment no longer had a positive effect on survival.

Limitations

The following limitations of cohort and registry studies have to be taken into consideration:

1) In study 2, we assume that few patients were lost due to misdiagnosed radiographs, as from 2002 computed tomography was used in Uppsala County. The CT protocols have a near 100% sensitivity (sensitivity for cervical spine plain radiography: 52%; sensitivity for CT: 98%) (Holmes and Akkinepalli 2005). All patients in our regional cohort study did have a C2 fracture (specificity 100%). The registry studies (Studies 3 and 4) started in 1997. Therefore, one can assume that in the five first years of the study, some C2 fractures could have been missed, but that the increase was largely due to an increase of odontoid fractures type 2 and 3. In the younger age group, a more differentiated panorama of C2 fractures was observed, including 24% Hangman’s fractures, 21% atypical fractures, 17% odontoid fractures type 3 and 34% odontoid fractures type 2. Thus, any conclusions regarding the distribution of C2 fracture subtypes in the younger population would be speculative in our study 3.

2) A selection bias could be assumed in Study 2, as the patients were treated in two highly specialized hospitals, but this selection bias would not lead to missed cases, as level one trauma centres are always contacted in the case of a fracture. However, it could be possible that patients in Uppsala and Malmö received more surgical treatment.
3) In a retrospective cohort study, a major limitation is cases lost because of incorrect coding or registration. The surgeons’ lack of knowledge of the field of spinal trauma or a perceived lack of time for proper coding reduces the quality of registration (O'Malley, Cook et al. 2005). Patients who do not seek medical assistance for their neck injury, or patients who have been treated outside the county in another hospital, could be missing from our dataset. The availability of a national patient registry with > 90% coverage of fracture cases allows for the proper identification of most C2 fracture cases in the investigated regions (Ludvigsson, Andersson et al. 2011).

4) The intra-observer reliability was 82% in Study 2 (unpublished data). It was performed on patients in Uppsala County with a primarily diagnosed odontoid fracture type 2 or 3.

5) The national population-based cohort design of Study 3 and 4 are superior to most previously published studies, since it minimizes the selection bias of highly specialized trauma centres, which often attract odd and unusual case referrals, thus distorting the disease panorama. Instead of creating a sample of the population, as you would do in randomized controlled trials, national cohort studies include the whole population.

6) ICD-10 does not allow for the sub-classification of C2 fractures. In a previous study from two regions in Sweden, we revealed that about 63% of C2 fractures are type 2 odontoid fractures in the elderly population aged ≥ 70 years, while 26% are odontoid fractures type 3; this means that a total of 89% of odontoid fractures in elderly patients are either type 2 or type 3.

7) Are we comparing ‘apples and pears’, when comparing the results of the incidence of C2 fractures with the results of the incidence of type 2 odontoid fractures? Even though we could demonstrate that 89% of C2 fractures in elderly patients are odontoid fractures, the type 3 fracture (about 26% of all C2 fractures) is almost always treated non-surgically. Therefore, in Studies 3 and 4, we compared the cohort of all odontoid fractures type 3 and non-surgically treated type 2 fractures with the cohort of surgically treated odontoid fractures type 2. An odontoid fracture type 3 is considered a ‘benign’ fracture. On the other hand, a recent study has identified odontoid fractures type 3 as a predictor of one-year mortality (Bajada, Ved et al. 2017). Unfortunately, the level of detail in the ICD-10: S12.1 code does not allow us to adjust for C2 fracture subtypes.

8) As the validity of the fourth digit of the fracture ICD-10 code (90%) is lower than the third digit (95%) (Bergström, Byberg et al. 2011), approximately 5% of C2 fractures were likely to be misdiagnosed as other cervical spine fractures (S12.0, S12.2, S12.7, S12.8 and S12.9). In contrast, the risk of non-C2 fractures being misdiagnosed as S12.1 is low, since the specificity of the S12.1 code was 100% (unpublished data).
9) A confounder that was not controlled for is the comorbidity of osteoporosis. If the population’s osteoporosis improved (i.e., due to better preventive healthcare measures), this would affect the risk of cervical spinal fractures.

10) As with most other countries, Sweden has a geographically, health-economically and ethnically unique population. The results presented in our studies might not be generalizable to the rest of the world. Studies from national patient registries in other countries will have to validate our results in their specific settings.

Randomized controlled studies are considered as providing the highest level of evidence, and were first introduced when streptomycin was evaluated as a treatment for tuberculosis (Council 1950). There are, however, some limitations of this type of study. The following limitations of a randomized controlled study have to be taken into consideration:

1) There are clear limitations in RCT protocols regarding generalizability. A randomized controlled trial has specific inclusion and exclusion criteria that are often restrictive. The RCT populations might not mirror the age or sex distribution of the target patient population. The RCT population is often healthier, more well-educated and of higher socioeconomic status (Murthy, Krumholz et al. 2004). This also means that in RCTs, patients are more likely to be adherent to the treatment. This may overestimate the effect of a treatment if it was introduced in the entire population.

2) Inadequate statistical power. The amount of time it takes to conduct RCTs, the difficulty in recruiting patients and the fact that they generally expect only small to modest differences in outcomes means that they are frequently underpowered when it comes to detecting important differences in outcomes. This can lead to the wrong conclusions being drawn, i.e., that there are no significant differences in treatments when a larger sample size would have uncovered significant differences. In the USOFT, which has NDI as a primary outcome, we have tried to adjust for the one-year mortality among patients aged ≥70 years with a non-surgical axis fracture treatment of 29%. Sixteen participants are needed in each group to reach 80% power with a two-sided significance level of \( p < 0.05 \) in a (clinically important) superiority study design. Adjusting for mortality, eight additional participants must be recruited into each group. This leads to the conclusion that a minimum of 24 subjects must be included in each group.

3) The RCT in this thesis employs an open-label design, according to which both the investigator and the patient know which treatment he or she will receive. Unfortunately, the open-label design has an inherent selection bias, as patients can drop out during enrolment or give informed consent prior to inclusion in this study.
4) A review of the allocation concealment methods used in studies in major medical journals in 2015 found that 19% of trials involved an inadequate allocation method and 22% did not appropriately report the randomization method (Clark, Fairhurst et al. 2016). Our protocol uses SNOSE allocation concealment and simple randomization. The sealed envelope technique requires good clinical practice and discipline on the part of the enrolling physician, since translucency and premature opening can corrupt the randomization process (Kennedy, Torgerson et al. 2017).

5) One-year progression-free survival and one-year all-cause mortality are common primary end points for RCTs. Due to the frailty of the geriatric study participants, the overlap of an unrelated and natural cause of death with injury-related mortality causes high variation, and would require a significantly greater sample size. Since HRQoL defines the value of life years gained, this study uses the NDI as its primary endpoint, with EQ-5D and survival as secondary endpoints.
Conclusions

I. No high-level evidence is available on the treatment of odontoid fractures type 2. Surgical treatment is superior to non-surgical treatment in patients aged between 65 and 85 years (quality of evidence: moderate). Posterior fusion has a higher bone fusion rate than other treatments (quality of evidence: low). Non-union is not correlated with a worse outcome (quality of evidence: low). There is no difference between non-surgical and surgical treatment when it comes to complications (quality of evidence: low).

II. Eighty-nine percent of C2 fractures in elderly patients are odontoid fractures type 2 or 3. There is an increased incidence of odontoid fractures type 2 and an increased proportion of them are surgically treated in two level-one trauma centres.

III. There has been an increased incidence of C2 fractures over the last decade, along with a decreased proportion of surgically treated elderly patients in Sweden.

IV. Surgery on C2 fractures is superior with regard to both short- and long-time survival. The age of 88 years was determined as a cut-off age after which surgery no longer had a positive effect on survival.

V. The RCT will provide the highest level of evidence regarding the treatment of type 2 odontoid fractures in the elderly population.
Clinical implications

The systematic review of the published evidence on odontoid fractures type 2 in elderly patients provided us with a scientific groundwork for further research.

The presentation of values for subgroup proportions allowed for further population-based research in which subgroup proportions have to be estimated from ICD-10 codes.

After one year, surgical stabilization improved survival with an RRR of 11%, which increased after two years to 19%. The fact that there was a 1.5 year longer survival period with surgical treatment is of relevance for health economic decision making, at a cost of four more days of hospitalization. Surgery lost its effectiveness on the survival of C2 fractured patients above the age of 88 years, after which surgery rather reduced the number of life years gained.

Previously published and ongoing studies are focused on non-union and mortality in relation to different treatment modalities. Nowadays, value-based care requires health-related quality of life (HRQoL) measures to influence health policy and decision makers. By studying the HRQoL and function of patients with odontoid fractures type 2, while also comparing the effectiveness of non-surgical treatment and surgical treatment (posterior C1-C2 fusion), we can address the cost-effectiveness of the treatment options.

Future studies should focus on timing of surgery, since waiting time to surgery may be an issue for complications. Subgroup analyses should investigate when is the best time to operate on odontoid fractures type 2. Furthermore, comparing the two approaches in posterior surgery (Goel-Harms and Magerl-Atlas claw fixation) regarding NDI and fusion rate, would elaborate the feasibility of these two posterior fixation methods. Since the proportion of patients above 90 years of age is growing, the non-surgical treatment recommendations have to be revisited, soon.
Kotfrakur i andra halsryggskotan hos äldre - Epidemiologi och behandling

En kotfraktur i andra halsryggskotan (C2) är en vanlig fraktur hos äldre, men även hos yngre. Mellan 9–18 procent av frakturerna i halsryggen är en C2-fraktur. C2-frakturer kan delas in i densfrakturer typ 1, 2 och 3, Hangman’s frakturer typ I, II, III, samt atypiska frakturer. 35–78% är densfrakturer, 11–25% Hangman’s frakturer och 14–20 % är atypiska frakturer. Fördelen skiljer sig mellan de yngre och de äldre patienterna, med en dominans för densfrakturer typ 2 och 3 hos de äldre. Hos de äldre är det benskörhetsfrakturer som är huvudorsaken, medan hos de yngre är det högenergivåld tex en trafikolycka, som är orsaken till en fraktur i C2.

Den här avhandlingen omfattar distribution, incidens, behandling, mortalitet samt ett protokoll för en randomiserad studie.


Vi startade C2 fraktur forskningen med en review artikel (Pek 1), för att sätta oss in i området. Vi fann bla att det saknades randomiserade kontrollerade studier och att den retrospektiva forskningen endast involverade ett fåtal patienter, men även att det råder delade uppfattningar om vilken behandling som egentligen är bäst för den här typen av frakturer hos äldre patienter.

Vi fortsatte därefter med att undersöka hur distribution och incidensen av axisfrakturer ser ut i en kohort i Uppsala och Malmö 2002–2014 (Pek 2). Vi fann bland de 233 patienterna, som ingick i studien, en stor andel (89%) och en signifikant incidensökning av densfrakturer typ 2 och 3 i den äldre patientgruppen ≥70 år. Vi fann även en trend mot kirurgisk behandling av densfrakturer typ 2.

För att utvärdera om det som vi funnit i de två universitetsstäderna, Uppsala och Malmö, även gäller för hela Sverige så fortsatte vi med en nationell
registerstudie med 6370 patienter (Pek 3). Där kunde vi se en tydlig incidensökning av C2 frakturer, men däremot en trend mot icke kirurgisk behandling av C2 frakturer förr i den äldre patientgruppen.

Samtidigt, vid den här typen av frakturer hos äldre har det i tidigare studier rapporterats om en hög mortalitet, både hos opererade och halskragebehandlade patienter. I det fjärde peket har vi därför undersökt (multiregisterstudie med 3375 patienter ≥ 70 år) om det är någon skillnad i mortalitet hos kirurgiskt och icke-kirurgiskt behandlade patienter med en C2 fraktur och funnit att mortaliteten är signifikant högre i den icke kirurgiskt behandlade gruppen. 1-års överlevnaden av kirurgiskt behandlade patienter är 81% och 72% för icke kirurgiskt behandlade patienter, med en relativ risk reduktion på 11%. När patienten når en ålder av 88 år så ses inte längre den effekten. Survivalanalyser är svåra att utföra i en randomiserad studie, med tanke på patientgruppen.

I en pågående randomiserad studie (USOFT) undersöker vi funktion och livskvalitet efter kirurgiskt/icke-kirurgisk behandling av densfrakturer typ2 hos äldre ≥75 års ålder. I avhandlingen beskrivs protokollet för RCT’n (Pek 5).
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To my parents, Gunlög and Pekka, thank you for your unconditional love and you always believing in me.

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My husband and co-supervisor, Yohan, although life has been tough on us, you have been able to support me, and giving me courage to continue my career. Without you this thesis would not have been possible.

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