Increased rate of reoperation in atypical femoral fractures is related to patient characteristics and not fracture type. A nationwide cohort study

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Abstract
Summary Atypical femoral fractures are burdened with a high rate of reoperation. In our nationwide analysis, the increased rate of reoperation was related to patient background characteristics, such as age and health status, rather than fracture type.

Introduction Patients with atypical fractures are complex to treat and burdened with a high risk of reoperation. We hypothesized that patients with surgically treated, complete atypical fractures have a higher risk of any reoperation and reoperation related to healing complications than patients with common femoral shaft fractures but that this increase would become insignificant when adjusted for predefined characteristics.

Methods A cohort of 163 patients with atypical fractures and 862 patients with common femoral shaft or subtrochanteric fractures treated from 2008 to 2010 and who had follow-up radiographs and register data available until 31 December 2014 was included. Reoperations were identified by a complementary review of radiographs and register data and were used to calculate risks for any reoperation and reoperations related to healing complications.

Results Patients with atypical fractures were more likely to be reoperated for any reason, age-adjusted OR 1.76 (95% CI, 1.08 to 2.86). However, patients with common fractures had a shorter follow-up due to a threefold higher death rate. Accordingly, in a multivariable-adjusted time-to-event model, the increased risk lost statistical significance for any reoperations, cause-specific HR 1.34 (95% CI, 0.85 to 2.13), and for reoperations related to healing complications, HR 1.32 (95% CI, 0.58 to 3.0). Continued use of bisphosphonate in the first year after the fracture did not affect the reoperation rate.

Conclusions Our findings suggest that the increased risk of reoperation after an atypical femur fracture is largely explained by patient characteristics and not fracture type.

Keywords Atypical femoral fracture · Bisphosphonates · Complications · Osteoporosis · Reoperation risk

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the skeleton leading to impaired fracture healing [6]. However, because the local healing capacity in the cortical bone of patients treated with surgical resection of an incomplete AFF (stress fracture that has not yet broken completely) appears normal [16], impairment of fracture healing is even less likely for the healing of complete AFFs [17]. Case studies reporting an increased risk of healing complications might have been distorted by other factors (e.g., patient background characteristics, drug treatment [18], and death [19]) rather than the atypical fracture itself and associated bisphosphonate treatment.

Radiographic evaluation of fracture healing is inconsistent, especially in a retrospective study design [20]. Reoperations, on the other hand, can be objectively recorded. Our primary aim was to test the hypothesis that the proposed increased risk of reoperation and specifically the increased risk for reoperations related to healing complications because there is no high-quality evidence to support dynamization as a means to improve fracture healing [24–26]. The time interval between the initial fracture and the main reoperation was calculated in days. We excluded 99 patients from the original cohort of 1124 patients because of incomplete radiographic imaging (n = 51), preexistent implants (n = 39), or other reasons (n = 9).

In a second step, we retrieved data from the Swedish National Patient Register (NPR) on every admission for each individual patient from the initial fracture admission until 31 December 2014. We only considered admissions with the discharge diagnosis S72, T84, T81, T93, M84, M80.9, and M96, combined with a surgical procedure code of the Swedish version of the NOMESCO classification of surgical procedures.
The comparison with register data yielded another 13 reoperations (AFF = 3, CFF = 10). These reoperations included 10 screw removals, one arthroscopy, one reoperation due to hemorrhage, and one unspecified reoperation. The final study cohort included 1025 patients (AFF = 163; CFF = 862).

**Registers**

In Sweden, all permanent residents are provided a unique personal identification number that allows complete linkage with all nationwide registers. Data on drug use were obtained from the Swedish Prescribed Drug Register [1, 21], including data on dispensing of bisphosphonates and oral corticosteroids before and after the fracture admission [19]. Drug treatment was defined as ever use. Discharge diagnoses were collected from the NPR from 1987 and for outpatient visits from 2001 until 31 December 2014 [1, 21]. Depending on type, the positive predictive value of diagnoses registered in the NPR ranges from 85 to 100% [27]. All diagnoses before the date of the fracture were included to calculate the individual weighted Charlson’s comorbidity index at baseline [28].

We determined dates of death after fracture events by linkage to the National Population Register of the Swedish Tax Agency. Calculated from the period of inclusion (years 2008 through 2010), the mortality rate was determined for up to 7 years (until 31 December 2014) after the fracture event. The study was approved by the regional ethical review board in Linköping, (DNR 2014/407-31, 2015/382-32).
Statistical analysis

The risk of reoperation was calculated for each fracture type. Furthermore, age-adjusted odds ratios (ORs, using unconditional logistic regression) and relative risks (RRs, using log-binomial regression) were calculated separately for any type of reoperation and those related to healing complications. Odds ratios and relative risks were then further adjusted for the following predefined variables: sex, Charlson’s comorbidity index, and corticosteroid treatment. In addition to risk assessments, we performed time-to-event analysis using Cox regression to estimate age and multivariable-adjusted cause-specific hazard ratios (csHRs) for any type of reoperation and those related to healing complications. Age-standardized incidence rates were calculated, by use of direct standardization and five-year age intervals, with the age distribution of CFF patients as a reference.

We used the group of patients with CFF as a control group because they were representative of the general population of patients with underlying vulnerability to fractures and refrained from matching to avoid the introduction of selection bias [29].

We performed competing risk analysis (as a sensitivity analysis) with death as the competing event due to known differences in mortality rate [19].

We additionally used stratified analyses to estimate the impact of use and non-use of bisphosphonates on the hazard for reoperation. Stratified multivariable-adjusted csHRs were calculated and are presented as a forest plot (Fig. 2). Stata (version 15) and IBM SPSS (version 25) were used for statistical analyses.

Results

Patient and implant characteristics are listed in Tables 1 and 2.

Reoperations

Any type of reoperation was performed in 28 (17%) patients with AFFs and in 73 (8%) with CFFs (Table 3). Reoperations related to healing complications were done in 9 patients with AFFs and in 23 with CFFs. Multiple reoperations were performed in 20 patients (8 AFF, and 12 CFF). The age-adjusted RR was 1.61 (95% CI, 1.07 to 2.43) for any reoperation and 1.69 (95% CI, 0.78 to 3.68) for reoperations related to healing complications. When further corrected for differences in the predefined variables (i.e., sex, Charlson’s comorbidity index, corticosteroid treatment), the RRs were attenuated to 1.41 (95% CI, 0.92 to 2.17) for any reoperation and to 1.41 (95% CI, 0.63 to 3.17) for reoperations related to healing complications.

Adjusting for differences in follow-up time and accordingly unequal death rates (19% vs. 58% in patients with common fractures), the multivariable-adjusted csHR for any reoperation was 1.34 (95% CI, 0.85 to 2.13). A similar HR, though with lower precision, was calculated for reoperations related to healing complications as outcome. Expectedly, the subdistribution HRs for a reoperation were quite similar to the relative risk estimates (Table 4).

Of the 163 patients with atypical fracture, 127 (78%) had received bisphosphonate treatment before the index fracture. Of the bisphosphonate users, 17 (13%) were reoperated for any reason; of the bisphosphonate non-

[Fig. 2] Stratified, multivariable-adjusted cause-specific hazard ratios (x-axis) for any reoperation

Hazard for reoperation (csHR, 95% CI)

- decreased
- increased
users, 11 (31%) were reoperated for any reason: multivariable-adjusted csHR 0.34 (95% CI, 0.14 to 0.81). The rate remained lower even when reoperations related to healing complications were compared: multivariable-adjusted csHR 0.13 (95% CI, 0.03 to 0.54).

In contrast to patients with atypical fractures, bisphosphonate users who had had a common fracture displayed an increase in the rate of reoperations related to healing complications, with a multivariable-adjusted csHR of 2.62 (95% CI, 1.03 to 6.68). The multivariable-adjusted csHR for any type of reoperation was 1.65 (95% CI, 0.92 to 2.98). Continued use of bisphosphonate in the first year after the index fracture was not associated with an increased risk of any type of reoperation, regardless of fracture type.

### Discussion

Consistent with our hypothesis, age-adjusted estimates showed an increased risk of reoperation in patients with atypical femoral fractures. This risk difference became substantially attenuated when predefined patient background characteristics and follow-up time were controlled.

Impaired fracture healing is one of the proposed clinical hallmarks of AFFs and was adopted as a minor criterion in the first ASBMR task force report [3]. Numerous case reports have described increased reoperation rates after an atypical fracture [5, 10, 30–33], in one study as high as 46% [11]. The criterion of delayed healing mainly referred to incomplete AFFs (stress fractures), with inhibition of direct bone healing (inhibition of targeted remodeling) suggested as a possible mechanism. This seems reasonable, because bisphosphonate treatment in animal models has shown accumulation of microdamage formation [34] and inhibited resorption of fracture surfaces in stress fractures [35]. Inhibited resorption was coupled with impairment of new bone formation thus leading to delayed fracture healing [34, 35]. However, when incomplete atypical fractures are excised by use of a full-thickness cortical bone biopsy, the cortical defect that remains heals by indirect fracture healing and the formation of new bone occurs at normal speed, despite long-term bisphosphonate treatment [16]. This is not surprising because in indirect fracture healing, with the formation of an external callus, bone formation is uncoupled from bone resorption. This type of fracture healing therefore is typically not affected by bisphosphonates [15]. The remodeling of the external callus on

### Table 1  Patient background characteristics

|                      | AFF       | CFF       |
|----------------------|-----------|-----------|
| N                    | 163       | 862       |
| Age, mean (SD)       | 76.6 (8.19)| 82.2 (9.58)|
| Sex                  |           |           |
| Male                 | 11 (6.7%) | 169 (19.6%)|
| Female               | 152 (93.3%) | 693 (80.4%)|
| Charlson’s comorbidity index, median (IQR) | 3 (1–5) | 3 (1–6) |
| Time to complication (years)
  , median (IQR) | 0.74 (0.46–1.2) | 0.64 (0.19–1.3) |
| Outcome              |           |           |
| No event             | 104 (63.8%) | 290 (33.6%) |
| Reoperation          | 28 (17.2%) | 74 (8.6%) |
| Death                | 31 (19.0%) | 498 (57.8%) |
| Time to death (years)
  , median (IQR) | 2.8 (1.9–4.2) | 1.9 (0.4–3.4) |
| Follow-up time (years)
  , median (IQR) | 4.5 (2.7–5.5) | 3.2 (0.9–4.9) |
| Bisphosphonate use before the fracture | 127 (77.9%) | 102 (11.8%) |
| Bisphosphonate use after the fracture
  (first year) | 110 (67.5%) | 127 (14.7%) |
| Bisphosphonate use before fracture,
  Duration (years), mean (SD) | 3.64 (1.1) | 2.34 (1.65) |
| Corticosteroid use    | 49 (30.1%) | 140 (16.2%) |
| Fracture location     | Subtrochanteric | Diaphyseal |
|                      | 25 (15.3%) | 559 (64.8%) |
|                      | 138 (84.7%) | 303 (35.2%) |

1 For those with complication; 2 For those who died during observation interval

### Table 2  Frequencies of implants used

| Implant         | AFF       | CFF       |
|-----------------|-----------|-----------|
|                 | N   | %      | N   | %      | N   | %      |
| AFN             | 138 | 84.7   | 616 | 71.5   | 754 | 73.6   |
| RFN             | 22  | 13.5   | 121 | 14.0   | 143 | 14.0   |
| Plate*          | 3   | 1.8    | 125 | 14.5   | 128 | 12.5   |
| Total           | 163 | 100    | 862 | 100    | 1025| 100    |

AFN antegrade femoral nail, RFN retrograde femoral nail
*any type of plate construct
the other hand is delayed by bisphosphonates, because it involves osteoclast-derived resorption of callus tissue followed by lamellar bone formation through osteoblasts. Complete atypical fractures heal through the mechanism of indirect fracture healing, which supports our hypothesis that healing of complete atypical fractures should not be affected by bisphosphonate treatment.

In more recent reports, rates of reoperation in AFFs are much lower, especially with the use of cephalomedullary nails [7, 8, 13, 36, 37]. Nonetheless, these recent reports describe a delayed union when using historic controls or the use of the conventional 6 months as the cut-off point for delayed healing [8, 38]. One study found an increased risk of complicated healing in AFF patients compared with controls, even when delayed healing was based not only on radiographic but also clinical signs [39]. Risk estimates in that study, however, were not corrected for differences in patient background characteristics. The inability to correct for differences in patient background characteristics is a potential shortcoming in previous reports comparing outcomes of AFFs with other fracture types. In our study, we were not able to directly evaluate differences in fracture healing and instead used reoperations associated with complicated fracture healing as an indirect measure. The use of this proxy might introduce selection bias because the true number of patients with complicated healing remains unknown and might differ between groups. Given the retrospective design, we were not able to validate this proxy or directly control for it. However, in contrast to previous reports, we were able to control for multiple confounding factors and survival time, by using adjusted risk and time-to-event analyses with correction of predefined variables. With these adjustments, differences in reoperation rates associated with complicated healing were modest.

For a number of reasons, reoperation rates could conceivably differ between the two fracture groups. Patients with atypical fractures might expose the implant to greater stress during the period of fracture healing because of their younger age and more active lifestyle [7, 40]. This selection might be an effect of drug channeling bias as a consequence of treating younger and healthier patients with bisphosphonates [41]. On the contrary, elderly patients with common fractures might not seek health care for a non-union or might be deemed unfit to undergo surgery. Such an effect is conceivable considering that more than half of the patients with common fractures died during the 4–7-year follow-up.

We observed a lower risk of reoperations in patients with atypical fractures treated with bisphosphonates compared with those without treatment, even in the multivariable-adjusted model. Little is known about this subgroup of patients expressing radiologic features of atypical fractures but without reported use of bisphosphonate. One possible explanation could be that patients without a history of bisphosphonate treatment suffer from undetected bone metabolic conditions with a predisposition for stress fractures and impaired fracture healing. Further investigations are needed to elucidate these differences. Continuation of bisphosphonate therapy during the first year after the fracture did not influence the risk of reoperation comparing atypical fractures with common fractures. These findings are in line with previous results [7]. A shorter treatment duration before the fracture has been suggested to decrease the risk of complicated healing [38, 39, 42]. However, sample sizes were small in those studies [38].

A main strength of our study is the nationwide coverage and complete linkage between high-quality registers and radiographic adjudication of fracture site and features in accordance with current ASBMR criteria and our rigorous identification of reoperations, using two complementary methods. Limitations include the observational study design and the potential for residual confounding or undetected selection mechanisms related to fragility not captured by our study design. Differences in such factors between the two fracture types would probably result in further attenuation of our estimates. Because the majority of the patients in our cohort are of Caucasian origin, our results should be extrapolated to other ethnic groups with some reservation, especially given that atypical fractures are coupled to ethnicity and biomechanical aspects of femoral geometry.

| Type of reoperation                                      | AFF (N = 163) | CFF (N = 862) |
|--------------------------------------------------------|---------------|---------------|
| Reoperations related to healing complication            |               |               |
| Revision from intramedullary nail to plate              | 1             | 8             |
| Revision from plate to intramedullary nail              | 1             | 5             |
| Intramedullary nail exchange                            | 7             | 7             |
| Hip arthroplasty in presence of non-union               | 0             | 3             |
| Other reoperations                                      |               |               |
| Partial implant removal                                 | 2             | 12            |
| Complete implant removal                                | 2             | 5             |
| Dynamization procedure                                  | 6             | 3             |
| Peri-implant fractures                                  | 8             | 21            |
| Hip arthroplasty due to osteoarthritis                  | 0             | 2             |
| Other                                                   | 1             | 7             |
| Total                                                   | 28            | 73            |

Table 3 Frequencies and types of reoperations
### Table 4

Differences in reoperation rates between atypical femoral fractures and common fractures of the femoral shaft based on different statistical methods. Odds ratios (ORs) calculated with binominal logistic regression. Cause-specific hazard ratios (csHRs) taking differences in follow-up time into account, using Cox regression. Subdistribution hazard ratios (sdHRs) using the fine and gray proportional subdistribution hazard regression (sdHR) model to control for differences in death rates between the groups. All with 95% confidence intervals (95% CI).

| Event as binary                  | Fracture type | No. events (N) | Risk | Age-adjusted OR (95% CI) | Multivariable-adjusted OR (95% CI) | Age-adjusted RR (95% CI) | Multivariable-adjusted RR (95% CI) |
|---------------------------------|---------------|----------------|------|--------------------------|------------------------------------|--------------------------|-----------------------------------|
| Reoperation                     | NFF           | 74             | 8.6% | Ref.                     | Ref.                               | Ref.                     | Ref.                              |
| Reoperation - healing complication | NFF           | 23             | 2.7% | ref.                     | 1.73 (0.76–3.92)                   | 1.61 (1.07–2.43)         | 1.69 (0.78–3.68)                   |
| Reoperation - healing complication | AFF           | 9              | 5.9% | ref.                     | 1.73 (0.76–3.92)                   | 1.61 (1.07–2.43)         | 1.69 (0.78–3.68)                   |

| Event as binary                  | Fracture type | No. events (N) | Risk | Age-adjusted csHR (95% CI) | Multivariable-adjusted csHR (95% CI) | Age-adjusted sdHR (95% CI) | Multivariable-adjusted sdHR (95% CI) |
|---------------------------------|---------------|----------------|------|----------------------------|--------------------------------------|--------------------------|--------------------------------------|
| Reoperation                     | NFF           | 2657           | 27.9 | Ref.                       | Ref.                                 | Ref.                     | Ref.                                 |
| Reoperation - healing complication | NFF           | 669            | 35.0 | ref.                       | 1.49 (0.95–2.33)                     | 1.69 (1.09–2.64)         | 1.49 (0.92–2.42)                     |
| Reoperation - healing complication | AFF           | 2826           | 8.1  | ref.                       | 1.55 (0.7–3.42)                      | 1.32 (0.58–3.0)          | 1.71 (0.76–3.85)                     |

*Adjusted by age (continuous), sex, cortisone use (yes/no), and Charlson’s comorbidity index (continuous)
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