Perspectives on outcome following hand and wrist injury in non-osteoporotic patients
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CHAPTER 9

General discussion, future perspectives and conclusions
GENERAL DISCUSSION, FUTURE PERSPECTIVES AND CONCLUSIONS

General objective
The general objective of this thesis was to gain insight in radiological measurements, clinician reported outcomes (CROs) and patient reported outcomes (PROs) following hand and wrist injuries in non-osteoporotic patients. We have aimed to report on the prevalence of posttraumatic arthritis (PA) in these young non-osteoporotic patients and to describe the association between radiological measures, CROs and PROs following distal radius fractures (DRFs). Our second objective was to report on CROs and PROs following perilunate (fracture) dislocations (PLD/PLFDs). In addition, we intended to validate several PROs in the Dutch translation for upper extremity injuries. Finally, the purpose of this thesis was to put outcomes in perspective by reporting on their clinical relevance.

Posttraumatic arthritis following distal radius fractures
Prevalence
From the systematic review and our studied cohort of non-osteoporotic patients presented in this thesis, we conclude that the prevalence of PA following a distal radius fracture (DRF) was high at medium to longterm follow-up (respectively 37%-50% with follow-up ranging 18 months-38 years and 32% with median follow-up 62 months). In our cohort, all patients with PA had grade I or II after a follow-up of 5 years [1]. Based on our results we suggest that PA is a progressive process and changes significantly over time (prevalence of PA 31% at ≤36 months and 64% with >36 months follow up, respectively) [2]. This is supported by Forward et al. who described a cohort of young patients following DRFs at a mean follow-up of 38 years [3]. Although they reported a comparable prevalence of PA, after this long follow-up duration the grading of PA was worse (all grade II or III). We state that it is of importance for the young patient to comprehend that PA develops and progresses over time following DRFs, in the light of an expected long active working life.

PA and the association with age
Basic scientific and clinical studies have shown that older age is an important risk factor for the development of PA due to age-related changes in articular chondrocytes which results in altered ability to respond to cartilage damage [4-6]. We have chosen to select a young group of patients to investigate the influence of hand and wrist injury, who have a long active life ahead of them, because we reckon they have higher functional demands than older patients. A reason of not finding an association between age and PA in our study, could be that we selected young patients with normal functioning articular chondrocytes. In contrast, other authors reporting on DRFs in patients with wider age ranges did show an association between older age and higher prevalences of PA up to 65% of PA after 6.7 years [1,3].
Radiological measurements

Articular incongruency. In the presence of articular surface incongruency and joint instability there is an abnormal loading of the cartilage and subchondral bone, which leads to progressive cartilage degeneration [7,8]. This can decrease the cartilage repair potential, forming an ongoing vicious cycle and resulting in progression of PA over time [4]. To avoid this vicious cycle, it has been advocated to treat intraarticular fractures with anatomical reduction and stable fixation of articular fragments, which consequently results in reduction of the cartilage surface [9]. The studies included in our systematic review reported that DRFs healed with a step-off > 2mm are associated with development of PA [1,10-15]. However, in our cohort study no statistically significant association between articular incongruency and PA was present. This may be explained by the fact that, although 56 patients had some articular incongruency, only in 7 patients this exceeded 2 mm at follow-up. In addition, the grading of PA might not be severe enough yet to prove an association with articular incongruency due to a relatively short follow-up period. With longer follow-up duration, other authors have described an association between articular incongruency and PA [3]. We therefore conclude that intraarticular incongruency should be diminished with adequate reduction and stable fixation, where applicable, should be pursued to avoid PA in this young non-osteoporotic patient cohort.

Ligamentous injury. DRFs in young patients most often result from high-energy trauma and therefore most often are intraarticular fractures, which are associated with concomitant ligamentous injuries [16-20]. Prevalences up to 98% of associated ligamentous injury with DRFs, mostly scapholunate (SL) ligament injuries, have been described [21,22]. Similar to the genesis of ligamentous injury in distal DRFs, in carpal injuries, SL ligament injury is the first stage in the injury cascade that takes place in perilunate (fracture) dislocations (PLD/PLFDs) and can result in joint instability (according to the mechanism as described by Mayfield (Chapter 1, Figure 2) [23,24]. Progress over time of this joint instability is known as scapholunate advanced collaps (SLAC) and is known to result in radiocarpal PA [20]. Unfortunately, SL injuries are difficult to diagnose on plain radiographs, as only Geissler type IV lesions are represented by a distance between scaphoid and lunate > 2mm due to a complete tear [20,21,25]. In our study population, 30 patients had SL-distances exceeding 2mm, but no association with PA was present. Mrkonjic et al. support our finding that associated scapholunate injury in patients following DRF does not have to result in PA by scapholunate advanced collapse after long-term follow-up [26]. They reported no SLAC and subsequent PA at 15 years following DRFs with arthroscopically proven SL injuries. They hypothesized that radiographic instability of the SL ligament is not necessarily presented with clinical instability as tested with the Watson shift test [27]. Clinical instability is dependent on which anatomical portion of the SL is injured; it is known that the dorsal portion is most important for stability as well as extrinsic dorsal stabilizers [28]. Partial rupture of the SL ligament (for instance the volar portion) does not necessarily result in clinical instability. In addition, possibly the healing potential of the SL ligament might add to regaining a clinical stable situation following DRFs [26].
Other radiological measurements. With regard to other radiological measurements as predictors for PA, literature reported conflicting results [3,11,29,30]. In our study, the only radiological measurement that was associated with PA was radial length. Patients with PA had a statistically significant longer radial length (1mm) in comparison to patients without PA. In addition, in the patients with PA, the radial length of the injured wrist was also significantly longer (1.2mm) in comparison to the uninjured wrist. However, these measurements fall within error magnitude as reported by Watson et al. and therefore might be explained by measurement error [31].

To our knowledge, no studies reported on longer radial length and the association with PA. In contrast, Forward et al. reported on radial shortening of 2mm resulting in a 2.4 times higher risk on PA than with no shortening in radial length with a mean follow-up duration of 38 years [3]. However, most studies included in the systematic review reported no significant association with shortened radial length and the development of PA [1,32,33]. The development of PA has multifactorial causes, such as increased stress on the articular surface that damages cells and matrices of articular cartilage and subchondral bone [4]. So adequate correction of the radial length radius following DRFs seems to be important to decrease the risk on PA. However, further research regarding the influence of radial length on the development of PA is mandatory.

PA and CROs.

aROM. The included studies in the systematic review reported conflicting results regarding the association between PA and active range of motion (aROM); four studies described a significantly diminished flexion or flexion/extension [2,13-15]. One study described poor supination [12] and five studies reported no statistically significant association between PA and aROM (Chapter 2) [34-38]. All included studies described small populations, which might be an explanation for the conflicting outcomes. To overcome this, pooled data analysis of the open source data of seven studies was performed, revealing that only the aROM measurement radial deviation was statistically significantly worse in patients with PA in comparison to patients without PA (mean difference 3°) [12,13,15,35,37,39,40]. This mean difference is however within error magnitude and might be explained by measurement error [31]. When analyzing our patient cohort (Chapter 3), patients with PA had clinically relevant (and statistically significant) diminished flexion/extension (12°) and ulnar/radial deviation (6.3°) [41]. Although our cohort was comparable to the cohorts in the studies included in the systematic review regarding age and fracture type, the included number of patients in the studies reporting on an association between PA and aROM were mostly smaller than ours. In addition, the length of follow-up differed extensively between the studies. These factors might be the reason for the different results reported in our study (Chapter 3) in comparison with the results reported in the studies included in the systematic review (Chapter 2). With the expected progression of PA and a long active life ahead in these young patients, the knowledge that diminished flexion/extension and ulnar/radial deviation can be expected following DRFs is of importance to these young patients and their treating clinicians.
Grip strength. PA was not associated with diminished grip strength measurements in young patients following DRFs. Grip strength does not seem to be a determinant of hand or wrist function alone, but merely a reflection of overall muscle strength of the entire upper limb [42].

PA and PROs
Little is written in literature on the association between PA following DRFs and PROs. In the cohort study presented in Chapter 3, patients with PA had significantly lower scores on the MHQ subscales ‘general functioning,’ ‘esthetics,’ ‘satisfaction’ and total MHQ score. In addition, the SF-36 subscale ‘physical functioning’ was statistically significantly lower in patients with PA. The question arises if these differences withhold clinical relevant changes. Unfortunately, to our knowledge, no Minimal Important Changes (MICs) have been reported for these PROs. For DASH and PRWE subscales and total scores reference MICs are available [43,44] and only the difference between patients with PA and without PA on PRWE subscale ‘pain’ exceeded the reported MIC. However, the validated Dutch language version of the PRWE (PRWE-NL) seems to measure a unidimensional trait, so reporting on the subscale ‘pain’ in the Dutch translated version is not advocated [45]. Therefore, reporting MICs for the PRWE subscales might not be advisable. Our results suggest that PA does not have a clinical relevant impact as perceived by patients based on results gathered from the DASH and PRWE. Another possibility is that these questionnaires might not be the right tools to differentiate between patients with limitations due to PA or without. As a consequence, in our opinion both questionnaires cannot be used to monitor progression of PA in patients who sustained a DRF. The statistically significant associations between PA and the MHQ and SF-36 suggest that PA does impact non-osteoporotic patients following DRFs. The MHQ seems a promising tool to differentiate between patients who do or do not experience limitations due to PA following hand and wrist injury. To gain better insight into the clinical relevance of PA, MICs regarding the MHQ and SF-36 should be obtained.

Radiological measurements
Evolution
Patients following DRFs did not show signs of changes in radiological measurements in the first 6 weeks post-injury (Chapter 4), which is remarkable. Neidenbach et al. stated that changes did occur in these first 6 weeks following DRFs [46]. One of the possible explanations for their finding was that in their study, unstable DRFs were treated with conservative management, resulting in early dislocation. In our study, DRFs with unstable characteristics were treated with open reduction and stable fixation according to the Dutch guidelines for treating DRFs [47,48]. The earlier mentioned study reported no radiological changes between 6 weeks and 1 year follow up [46]. In contrast, our study did suggest that ulnar variance and radial inclination increased and step-off and gaps diminished statistically significantly during 5 years following DRFs. However, all these changes were minimal (≤ 1mm or ≤ 1°) and did not exceed reported error magnitudes suggesting they might be classified as measurement error [31].
If ulnar variance and radial inclination increase, but radial length does not increase, a compression (and relative shortening) of the ulnar side of the distal radius must be present. Rikli and Regazzoni described this anatomical area in 1996 as the intermediate column [49,50]. It consists of the lunate facet and the sigmoid notch and is responsible for >50% of the axial compressive forces that are transmitted across the wrist during normal activity [51]. Brink and Rikli acknowledged the importance of the intermediate column and described the volar and dorsal ‘key corner’ of the intermediate column. They stated that control with reduction and stable fixation of this ‘key corner’ should be the first step of the surgical strategy after a DRF, because insufficient treatment may result in joint instability and carpal subluxation [50]. The changes over time as presented in our study might be the result of some instability of this ‘key’ corner, although changes were minimal.

As stated earlier, step-offs and gaps seemed to diminish over time in our study. Residual step-offs and gaps with concomitant cartilage injury have been related to insufficient remodelling processes of subchondral bone leading to the development of PA [52]. In contrast, animal studies have suggested that the extent of incongruency following intraarticular fractures might diminish due to cartilage and subchondral bone remodelling responses [53]. To our knowledge, no literature on a decrease in articular incongruency in adult patients is available. Bone healing is a complex event that involves coordination of two complex forces: anabolism or tissue formation and catabolism or remodelling under influence of axial, translational and rotational forces [54,55]. Possibly a form of remodelling diminishes the articular incongruence, but further research is mandatory.

Reference values
Mean radiological measurements at follow-up of the reported DRFs in this thesis were within reported normal ranges, although several patients did have radiological measurements exceeding reference values. Normal reference values regarding radiological measurements following DRFs have been reported in literature (Chapter 1, Figure 3) [56-64]. Some studies reported on small populations and were published between 1976 and 2018 with most likely varying quality of radiographic imaging over time. To overcome the shortcomings of comparing radiological measurements with reported reference values, we have used the measurements of the uninjured wrist as a reference to ensure correction for anatomical variation between patients. Of all radiological measurements, only a statistical significantly more pronounced dorsal angulation was present in the injured wrist compared to the uninjured wrist (Chapter 4). This measurement change did not exceed reported error magnitude [31] and thus might be explained by measurement error. Our results may suggest that adequate treatment has been provided to the patients, but may also suggest that the reported reference measurements have such wide ranges that patients in our study only exceeded reference values minimally. More importantly, the question arises what the clinical implications of radiological measurements
are. Acceptable alignment has not been defined yet in terms of clinical relevance. The reported reference values for radiological measurements following DRFs might not reflect the thresholds for a clinical relevant impact on outcomes. We suggest the use of radiological measurements of the uninjured wrist as reference. We advise to determine minimal important changes (MICs) regarding radiological measurements to put reference values in perspective in terms of clinical relevance.

**Radiological measurements, CROs and PROs**

The associations between PA, residual articular incongruency and worse outcome regarding aROM and PROs seem to be complex. Regarding radiological measurements, only step-off was associated with diminished flexion/extension, radial/ulnar deviation and worse SF-36 ‘mental component’ score with statistical significance (Chapter 4). In addition, we have shown that articular incongruency was associated with PA. Also, PA was associated with worse aROM measurements and PROs (Chapter 2-3). In addition, diminished aROM measurements were associated with diminished PROs (Chapter 3). Because our population was relatively small, we have chosen not to compare patients who can be categorized within or out of radiological reference values as reported in literature. A recent systematic review regarding the association between radiological measurements and PROs following DRFs has hypothesized that radiological measurements exceeding reported reference values (Chapter 1, Figure 3) are less well tolerated by young active patients in comparison to patients older than 60-65 years of age [65]. The two included studies that stratified for age showed a clinically relevant difference between acceptable and unacceptable alignment regarding the PRWE and DASH scores for patients younger than 60-65 years and not in older patients [66,67]. Besides step-off, the radiological measurements in our study might not have been pathological ‘enough’ to show associations with PROs.

**Clinician reported outcomes**

*Active range of motion*

Flexion/extension and radial/ulnar deviation seem to be cinically relevantly diminished following DRFs and PLD/PLFDs in our groups of young non-osteoporotic patients when comparing these CROs to healthy controls, but also when comparing outcomes to the uninjured wrist (Table 1 & Chapter 3-5) [41]. Although not statistically tested, PLD/PLFD patients seem to have worse aROM measurements than patients following DRFs (Table 1). This may imply that a PLD/PLFD is a more severe injury with poor functioning in comparison to a DRF. For DRF patients, diminished aROM was associated with PA and articular incongruency (Chapter 3-4). For the patients following PLD/PLFDs we could not calculate such associations due to the limited sample size (Chapter 5). However, it is known that PLD/PLFDs may lead to PA due to joint instability resulting in SLAC [68-70]. This could be an
explanation for the diminished aROM measurements in these patients. Karagiannopoulos et al. are the only authors reporting on MIC regarding aROM following DRFs using an anchor-based method (N= 33, mean age 59.7 years, follow-up 8-12 weeks) [41]. No MICs were reported for ulnar/radial deviation or pro/supination. The target population was comparable to our population, although the reported population was older than non-osteoporotic age ranges and the sample size was small. We hypothesize that younger patients may have even lower thresholds for noticing a decrease in aROM in every day life, because of their high demand of hand and wrist function. MICs for all aROM measurements need to be calculated in a younger population following DRFs and PLD/PLFDs, to determine actual clinical relevance of diminished function of hand and wrist for this cohort. When counselling patients regarding their hand or wrist injury and the expected outcome, it should be pointed out that diminished aROM can be expected.

**Grip strength**

Following DRFs no clinical relevant change in grip strength measurements was observed when comparing outcomes to the grip strength measurements of the uninjured wrist (Table 1 & Chapter 3). However, within the PLD/PLFD patients clinically relevantly diminished grip strength was present when comparing outcome with measurements of the uninjured wrist. This result remained present when excluding the patients receiving a wrist arthrodesis (Chapter 4). Again, this accentuates that a PLD/PLFD seems to be an injury with more severe consequences than a DRF. For DRFs, only grip strength was statistically significantly associated with shorter radial length (Chapter 4). Several reports have mentioned an association between radial shortening and diminished grip strength measurements [1,71-74]. Radial shortening can cause an increased pressure in the distal radio-ulnar joint (DRUJ) and a shift in the centre of pressure within the sigmoid notch and impact grip strength in a negative manner [75-77]. We hypothesize that radial length as measured in our study was not pathological enough to show statistically significantly diminished outcomes. In addition, it has been reported that grip strength is not a determinant of hand or wrist function alone, but merely a reflection of overall muscle strength of the chain of muscles of the upper limb [42]. In this light, our results regarding the PLD/PLFD patients are remarkable. We hypothesize that the limitations following PLD/PLFDs results in disuse and subsequently diminished overall muscle strength of the injured arm. Kim et al. presented the only research on MICs regarding grip strength measurements in 50 patients treated for a DRF with volar locking plate fixation using an anchor-based method at 1 year follow up [78]. Although the target population was comparable to our population, the sample size was small and ages were not reported. MIC values for grip strength measurements, such as power grip, sustained grip and key pinch grip, need to be calculated in larger patient populations with specific stratification for age, gender and injury characteristics to enable better interpretation of CROs. This can determine actual clinical relevance of grip strength for this cohort.
Chapter 9

Patient reported outcomes
From our studied cohort following DRFs, the PRWE was clinically relevantly diminished (Chapter 4). We concluded that some PROs are statistically significantly diminished in patients with PA and with residual articular incongruency (Chapter 3). In addition, substantial differences regarding PROs were encountered between patients with DRFs and PLD/PLFDs and exceeding MICs (Table 2). We may conclude that the latter patients seem to suffer more limitations, although we only investigated a limited sample size. PROs are becoming increasingly important to report on outcome following hand and wrist injuries. Several authors have advised to report core sets of outcome measures (including CROs and PROs) to facilitate comparing outcomes reported in literature [80,81]. However, for clinical practice, these core sets seem too extensive and thus too time-consuming. Therefore, we advise a more practical version. The question arises which PRO to implement in this ‘lean’ core set?

It is important to understand what a PRO is actually measuring and if it is measuring the same construct as it was designed to do. It is known that by translating a PRO, the designed construct to be measured can change. Therefore, validation studies are necessary following translation. The original constructs of the DASH and the PRWE were designed to measure multiple subscores in the English language [82-84]. We concluded that the DASH-Dutch Language Version (DASH-DLV) measures a unidimensional trait in patients with upper extremity injuries and should be reported as a single score (Chapter 6). In addition, the Dutch version of the PRWE (PRWE-NL) has been validated by our research group and it was concluded that the PRWE-NL also measures a unidimensional trait in patients with upper extremity injuries [45]. Therefore, single scores

### Table 1. Comparison of CROs of the studies of this thesis

<table>
<thead>
<tr>
<th>CROs</th>
<th>DRF patients (N=73)</th>
<th>Uninjured wrist DRF patients</th>
<th>Mean difference DRF</th>
<th>PLD/PLFD patients (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
<td>Range of motion (*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexion/extension</td>
<td>141 (18)</td>
<td>153 (13)</td>
<td>-11.2 (12.6)*</td>
<td>90 (27)</td>
</tr>
<tr>
<td>Ulnar/radial deviation</td>
<td>58 (11)</td>
<td>65 (11)</td>
<td>-6.9 (9.9)</td>
<td>33 (14)</td>
</tr>
<tr>
<td>Supination/pronation</td>
<td>147 (13)</td>
<td>152 (11)</td>
<td>-5.3 (11.0)</td>
<td>155 (12)</td>
</tr>
<tr>
<td>Grip strength measurements (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grip strength</td>
<td>43.5 (13.2)</td>
<td>46.1 (12.7)</td>
<td>-2.6 (6.0)</td>
<td>35.3 (16.0)</td>
</tr>
<tr>
<td>Sustained grip strength</td>
<td>24.6 (10.9)</td>
<td>25.0 (9.6)</td>
<td>-4.6 (6.4)</td>
<td>22.3 (11.9)</td>
</tr>
<tr>
<td>Key pinch strength</td>
<td>8.5 (2.8)</td>
<td>8.7 (2.5)</td>
<td>-1.0 (2.0)</td>
<td>8.5 (1.7)</td>
</tr>
</tbody>
</table>

N=number of patients, CROs=clinician reported outcomes, DRF=distal radius fracture, PLD/PLFD=perilunate (fracture) dislocation, MIC=minimal important change, °=degrees, kg=kilograms, *=difference exceeding MIC
should be reported when using the DASH-DLV and PRWE-NL. The QuickDASH was validated in the Dutch language for patients with elbow dislocations [85], but not for patients with hand and wrist injuries. The MHQ has not been validated in the Dutch translated version. Our goal is to perform this in the near future. The SF-36 has been validated in the Dutch language in a general population and the authors concluded that it had acceptable validity [86]. However, statistically significant differences in mean scores were observed as a function of age, gender and the prevalence of chronic health conditions [86]. This supports our hypothesis that younger patients might score differently on PROs than older patients. To our knowledge, the SF-36 has not been validated in patients with hand and wrist injuries. The PROMIS Physical Function – Upper Extremity v2.0 (PROMIS UE v2.0) item bank, containing 46 items, was specifically designed for upper extremity disorders [87,88]. It has been translated to the Dutch language and validated (Chapters 7 and 8). We concluded that it measured a unidimensional trait. Following Item Response Theory, the Dutch-Flemish PROMIS UE v2.0 (DF-PROMIS-UE v2.0) item bank is now ready for Computer Adaptive Testing (CAT). CAT uses an algorithm that reduces the number of questions that need to be answered and therefore diminishes the burden for patients. In addition, the standard DF-PROMIS-UE v2.0 7-item short form consisting of 7 pre-determined questions showed sufficient psychometric properties. Age was not a determinant of outcome, i.e. younger patients did not answer items different than older patients. Patients with hand/wrist problems scored worse on items regarding fine tactile function, while patients with shoulder/arm complaints scored worse on items regarding heavy lifting tasks. The impact on the total score, however, was negligible because the biases cancelled each other out. Our results from the validation studies suggest that outcome as measured with PROs might not necessarily

<table>
<thead>
<tr>
<th>Uninjured wrist PLD/PLFD patients</th>
<th>Mean difference PLD/PLFD</th>
<th>Mean difference DRF – PLD/PLFDs</th>
<th>Healthy controls (N=22)</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
<td>144 (16)</td>
<td>-54 (34)*</td>
<td>51</td>
<td>150 (20)</td>
<td>5.0-7.1 [41]</td>
</tr>
<tr>
<td>61 (10)</td>
<td>-29 (13)</td>
<td>25</td>
<td>61 (12)</td>
<td></td>
</tr>
<tr>
<td>162 (9)</td>
<td>-8 (9)</td>
<td>-8</td>
<td>164 (14)</td>
<td></td>
</tr>
<tr>
<td>48.0 (13.0)</td>
<td>-12.7 (10.4)*</td>
<td>8.2</td>
<td>45.1 (14.3)</td>
<td>6.5 [78]</td>
</tr>
<tr>
<td>30.0 (10.2)</td>
<td>-7.6 (9.8)</td>
<td></td>
<td>29.6 (10.6)</td>
<td></td>
</tr>
<tr>
<td>9.2 (2.4)</td>
<td>-7 (1.6)</td>
<td></td>
<td>9.0 (2.4)</td>
<td></td>
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</tbody>
</table>

Table 1. Comparison of CROs of the studies of this thesis.
be comparable between patient populations with different characteristics and with different disorders. In Chapter 7, we concluded that the construct validity of the DF-PROMIS-UE v2.0 was good with high correlations with all legacy instruments: DASH, PRWE and MHQ-ADL. This suggests that the DF-PROMIS-UE v2.0 could replace the more extensive PROs that have been validated in the Dutch language; the DASH-DLV and PRWE-NL. This might be promising for our suggested lean core set. The DF-PROMIS-UE v2.0 CAT or 7-item short form are also less time consuming, which is important for implementation in clinical practice. However, some differences in reliability between the PROs were found. The DASH and MHQ-ADL displayed better reliability than the DF-PROMIS-UE v2.0 standard CAT and 7-item short form. The MHQ-ADL was less reliable than the DF-PROMIS-UE v2.0 CAT and 7-item short form in patients with poor upper extremity functioning (Chapter 8). In addition, The DF-PROMIS-UE v2.0 CAT is on average more efficient than the DF-PROMIS-UE v2.0 full item bank and 7-item short form and more efficient than the DASH, QuickDASH and MHQ (Chapter 8). This should be taken into account when interpreting these PROs in clinical practice. Because the PRWE was not administered in half of the population, we have not been able to perform reliability and efficiency analyses for the PRWE and PROMIS-UE v2.0 item bank, unfortunately. From our cohort studies, the MHQ seemed to provide more discriminative ability with substantial differences in scores between patients following DRFs with and without PA or in PLD/PLFD patients in comparison with healthy controls. For clinical practice, a reliable PRO with low burden for the patient is desirable, such as the MHQ-ADL, QuickDASH, PROMIS-UE v2.0 7-item short form and CAT methodology comprise of 7, 11, 7 and 4-7 items respectively.

If considering inclusion of a PRO in a ‘lean’ core set of measurements following hand and wrist injuries, the following should be taken into account: DASH and PRWE are PROs with an extensive number of items, which may be considered too much for use in daily clinical practice; MHQ has not been validated in the Dutch language yet and has no reported MICs for hand and wrist injuries; the translated version of the QuickDASH has not been validated for Dutch patients with hand and wrist injuries; the PROMIS-UE v2.0 item bank has no reported MICs yet. As such, it is not easy to advise on a lean version of a core set. For the time being, we advise to use the DASH and PRWE. We reconsider this advice if MICs have been determined for the PROMIS-UE v2.0 item bank and MHQ or if MHQ and QuickDASH have been validated in the Dutch translated versions for this specific patient cohort.

**Minimal important change**

Assessing patient progress has become an integral part of clinical practice nowadays. Meaningful threshold change values of outcome tools are essential for guidance and decision-making regarding a patient’s treatment and rehabilitation strategies. Having clear values for MICs regarding PROs for hand and wrist injuries will facilitate clinical interpretation and optimal communication with individual patients regarding their outcome. The differences in PROs reported in this study
between the healthy controls, patients following DRFs and patients following PLD/PLFDs are substantial and exceed reported MICs, indicating substantial impairments in daily life (Table 2). Note however that MICs are thresholds to determine clinical relevant changes as perceived in individual patients and not between groups. Terwee et al. state that interpretation of MICs should be done with caution due to different methodology and differences between patient cohorts [89]. Let us take a closer look at what we do know regarding MICs for the PRO scores reported in this thesis. Franchignoni et al. used a combination of anchor- and distribution-based methods to calculate the MIC for the DASH in 255 patients (mean age 49 years, SD 15) with upper extremity injuries of which 9% comprised of DRFs [43]. Walenkamp et al. calculated the MIC of the PRWE subscales and total scores on 102 Dutch patients (median age 59 years, IQR 48-66) following DRFs using anchor-based methods [44]. Shauver et al. used an anchor-based method to determine MIC of the MHQ for patients with carpal tunnel syndrome, reumatoid arthritis and DRFs [90]. The variation of the MICs for patients with carpal tunnel syndrome and reumatoid arthritis were substantial, supporting the theory that MICs should not be extrapolated between different patient cohorts. Due to ceiling effects for the DRF patients at the 3 months assessment, none of the MHQ domains showed discriminative ability [90]. Possibly this patient population was ‘too good’ to show discriminative ability and further research with larger populations is mandatory. For the SF-36, no MICs regarding upper extremity injuries have been calculated to our knowledge. We conclude that various methods have been used to determine MICs in literature, which might result in non-comparable MICs. In addition, MICs should not be extrapolated between different patient cohorts and therefore we hypothesize younger patients might have lower MIC thresholds to notice impairment. Further research is mandatory to determine clinical relevance in specific patient populations stratified for age and injury for all PROs reported in this thesis.

**Strengths and weaknesses**

One of the innovative aspects of this thesis is the specific inclusion criterion regarding age of the patient cohort. We have specifically tried to gain insight in a non-osteoporotic age group, since we believe they have high demands of the function of their hand and wrist following injury. The systematic review described in this thesis is the first to our knowledge to report on outcomes in this patient group.

Radiological measurements, CROs and PROs were concisely obtained with validated measurement protocols and are therefore reproducible. All radiographs were evaluated by a single radiologist specialized in musculoskeletal disorders with a special interest in hand and wrist anatomy; For CROs (aROM and grip strength) we used the same measurement protocol for all studies. For PROs we used the DASH, PRWE, MHQ and SF-36 for all cohort studies. As such, we produced manuscripts with specific information on a core set of CROs and PROs as have been suggested to report on when reporting on outcome following DRFs [80,81].
Table 2. Comparison of PROs of the studies of this thesis

<table>
<thead>
<tr>
<th>PROs</th>
<th>DRF patients (N=73)</th>
<th>PLD/PLFD patients (N=11)</th>
<th>Mean difference DRF – PLD/PLFDs</th>
<th>Healthy controls (N=22)</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>DASH</td>
<td>9 (12)</td>
<td>22 (20)</td>
<td>13</td>
<td>3 (6)</td>
<td>10.8 [43]</td>
</tr>
<tr>
<td>PRWE</td>
<td>Pain</td>
<td>9 (11)</td>
<td>19 (14)</td>
<td>10</td>
<td>1.5 [44]</td>
</tr>
<tr>
<td></td>
<td>Function</td>
<td>10 (15)</td>
<td>19 (28)</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>14 (17)</td>
<td>31 (22)</td>
<td>17</td>
<td>11.5</td>
</tr>
<tr>
<td>MHQ</td>
<td>General function</td>
<td>74 (19)</td>
<td>59 (16)</td>
<td>15</td>
<td>94 (9)</td>
</tr>
<tr>
<td></td>
<td>Activities general life</td>
<td>90 (15)</td>
<td>84 (13)</td>
<td>14</td>
<td>99 (2)</td>
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<tr>
<td></td>
<td>Work</td>
<td>87 (21)</td>
<td>89 (20)</td>
<td>2</td>
<td>100 (0)</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>85 (20)</td>
<td>71 (26)</td>
<td>14</td>
<td>98 (4)</td>
</tr>
<tr>
<td></td>
<td>Esthetics</td>
<td>92 (15)</td>
<td>91 (11)</td>
<td>1</td>
<td>97 (11)</td>
</tr>
<tr>
<td></td>
<td>Satisfaction</td>
<td>77 (26)</td>
<td>63 (30)</td>
<td>14</td>
<td>99 (2)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>84 (16)</td>
<td>76 (15)</td>
<td>8</td>
<td>98 (3)</td>
</tr>
<tr>
<td>SF-36</td>
<td>Physical functioning</td>
<td>92 (12)</td>
<td>86 (9)</td>
<td>6</td>
<td>93 (15)</td>
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<tr>
<td></td>
<td>Social functioning</td>
<td>90 (19)</td>
<td>80 (31)</td>
<td>10</td>
<td>95 (12)</td>
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<tr>
<td></td>
<td>Role model physical problem</td>
<td>86 (28)</td>
<td>61 (41)</td>
<td>25</td>
<td>88 (30)</td>
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<tr>
<td></td>
<td>Role model emotional problem</td>
<td>90 (27)</td>
<td>85 (35)</td>
<td>5</td>
<td>95 (21)</td>
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<tr>
<td></td>
<td>Mental health</td>
<td>83 (13)</td>
<td>75 (19)</td>
<td>8</td>
<td>89 (11)</td>
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<td>Vitality</td>
<td>71 (18)</td>
<td>67 (21)</td>
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<td>82 (15)</td>
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<tr>
<td></td>
<td>Pain</td>
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<td>68 (22)</td>
<td>13</td>
<td>90 (14)</td>
</tr>
<tr>
<td></td>
<td>General health experience</td>
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<td>67 (11)</td>
<td>6</td>
<td>78 (14)</td>
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<tr>
<td></td>
<td>Health change</td>
<td>52 (20)</td>
<td>45 (10)</td>
<td>7</td>
<td>51 (14)</td>
</tr>
</tbody>
</table>

n=number, PROs=patient reported outcomes, DRF=distal radius fracture, PLD/PLFD=perilunate (fracture) dislocation, MIC=minimal important change, DASH=disability of arm, shoulder and hand, PRWE=patient reported wrist evaluation, MHQ=michigan hand questionnaire, SF-36=short-form 36

Not only have we reported on statistical significance, but more importantly on clinical relevance by comparing outcomes with MICs as reported in literature. This has been scarcely performed in literature regarding hand and wrist injuries. Being able to extrapolate results as presented in this thesis to clinical practice is important. We believe we have contributed to clinicians’ and patients’ interpretation of CROs and PROs following hand and wrist injury in everyday clinical practice and this can guide treatment and rehabilitation strategies.
General discussion, future perspectives and conclusions

It has to be acknowledged that the included studies in the systematic review describe small cohorts of patients. In addition, the same is true for our clinical studies. Also, a selection bias may have been present in our clinical studies, since our response rate was low. Conclusions regarding radiological measurements, CROs and PROs should therefore be interpreted with caution. Adequate sample sizes were used to validate the DASH-DLV, PRWE-NL and DF-PROMIS-UE v2.0. The reference values, error magnitudes and MICs reported in literature that we have used as references for CROs and PROs have been calculated mostly with (different) anchor-based methods in small patient cohorts that are not completely comparable [31,41,43,44,78,90]. This implies care should be taken when drawing conclusions and further research is necessary.

Clinical implications

Most important knowledge for young non-osteoporotic patients and their primary treating clinicians is that flexion/extension and ulnar/radial deviation following DRFs and/or PLD/PLFDs have a high chance of being impaired to such an extent that patients will notice this in daily life. For patients following PLD/PLFDs these impairments seem to be worse than for patients following DRFs. Grip strength most likely is not affected for patients following DRFs (except those with radial shortening), but is clinically relevantly impaired in patients following PLD/PLFDs. Consequently, hand and wrist injuries can evolve in a major life event for a patient. At their visit to the surgical emergency department, it is therefore mandatory that patients receive adequate consultation and information regarding the characteristics of the injury and the expected outcomes. Following DRFs, PA and residual articular incongruency are main factors impacting range of motion and PROs. In addition, adequate correction of radial length seems important to decrease the risk of PA. Therefore, treatment strategies should be aimed at limiting articular incongruency to a minimum and correct radial length adequately in this patient population. Reference radiological measurements should be used with caution and we advise to use a radiograph of the uninjured wrist to put measurements in perspective and correct for anatomical variation.

Since hand and wrist injuries can evolve in major life events for patients, due to the possible impairment in daily life, we advise organisation of a specialized team dedicated to hand and wrist injuries including trauma surgeons, orthopaedic surgeons, plastic surgeons, rehabilitation physicians, radiologists and hand therapists. This multidisciplinary approach ensures the best possible primary treatment, but also facilitates optimal rehabilitation treatment to diminish future impairment to a minimum. In addition, it can help patients cope with residual diminished function and provide them with options for adjustments in daily life if needed.
For the individual patient it would be beneficial to get insight in their own progress following rehabilitation and in reference values of our suggested ‘lean’ core set of CROs and PROs from patients with a comparable age and injury. This way, a patient can gain realistic expectations of outcome following their hand and wrist injury. With actively involving individual patients in the treatment and rehabilitation process following an injury, this will add to achieving the best possible outcome.

**Future perspectives**

We would advise to create a database of non-osteoporotic patients following hand and wrist injury consisting of patient characteristics (i.e. age, gender, intensity of occupation, intensity of sports/hobbies), injury characteristics (i.e. type of injury, radiological measurements, open/closed injury, type of treatment) and CROs and PROs at several follow-up moments (baseline, 6 weeks, 3 months, 6 months, 1 year). Preferably, multicenter inclusion should be organized. Data should be collected in data repositories. The burden for patients and clinicians should be minimized. When patients consent to participating, most patient and injury characteristics can be retrieved from the digital patient system. Using an app or link for patients to fill in their missing patient characteristics (such as intensity of occupation and hobbies), using digital measurement systems for measuring CROs and using ‘lean’ PROs (for example the QuickDASH or PROMIS-UE v2.0 CAT or 7-item short) adds to diminishing the burden for patients. The database has multiple purposes.

Firstly, patients will be able to gain insight in their own progress during rehabilitation. Comparison to outcome reported for comparable patients from the database, puts outcome in perspective. For the treating clinician, this information can serve as a tool for transparent communication regarding expected outcome.

Secondly, the database can function as a quality registration. Annual reports on CROs and PROs of the included patients will enable transparency regarding differences in outcome between treating clinicians and centers.

Finally, with multicenter collection of data in the advised database, high quality research is possible. For example, calculating MICs of CROs and PROs for specific populations will be feasible. There is a need to determine the minimal change in a score that patients consider of importance for several outcome measures following hand and wrist injuries. We aim to calculate MICs regarding all CROs and PROs mentioned in this thesis for hand and wrist injuries in young non-osteoporotic patients.
Conclusions
We have aimed to put outcomes following hand and wrist injury in young non-osteoporotic patients in a clinically relevant perspective. PA had a relatively high prevalence following DRFs and progressed over time. Radiological measurements following DRFs evolved over time, but probably not with a clinical relevant impact within a follow-up period of five years. Diminished flexion/extension and ulnar/radial deviation is present following DRFs and PLD/PLFDs. Grip strength is clinically relevantly diminished in patients following PLD/PLFDs, but not in patients following DRFs. Associations between the presence of PA and diminished range of motion and diminished outcome on several PROs were present. Residual articular incongruency was associated with PA, diminished range of motion and possibly with diminished health status. Therefore, residual articular incongruency needs to be minimized by adequate reduction and (surgical) stabilization of DRFs to diminish the risk of development of PA in these young non-osteoporotic patients. Reported reference measurements do not seem to withhold clinical relevant thresholds. We suggest that measurements of the uninjured hand or wrist could be used to correct for anatomical variation. We conclude that the translated versions of the DASH, PRWE and PROMIS-UE v2.0 item bank have been adequately validated for Dutch patients with hand and wrist injuries. For clinical practice, we advise to use a ‘lean’ version of a core set of outcome measures; flexion/extension, ulnar/radial deviation and either the DASH or PRWE. In the future, after calculation of MICs, the PROMIS-UE v2.0 seems a promising tool to incorporate in this core set. We aim to validate the Dutch translated versions of the MHQ and SF-36 and to report on MICs for the DASH, QuickDASH, PRWE, MHQ, SF-36 and PROMIS-UE v2.0 item bank for young non-osteoporotic patients following hand and wrist injury. This will enable implementation of low burden PROs in ‘lean’ core sets to interpret outcome in clinical practice.
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