Fractures of the distal radius

Factors related to radiographic evaluation, conservative treatment and fracture healing

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Distal radius fractures (DRFs) are one of the most common injuries encountered in orthopaedic practice. Such fractures are most often treated conservatively, but surgical treatment has become increasingly common. This trend is not entirely scientifically based.

The aims of this thesis were threefold: to increase measurement precision in dorsal angulation (DA) on radiographs and computer tomographies (CTs); to assess the results after shortened plaster cast fixation time in reduced DRFs; and to evaluate the feasibility and safety of applying Augment® (rhPDGF-BB/β-TCP) in DRFs.

In Paper I and Appendix 1 and 2, a semi-automatic CT-based three-dimensional method was developed to measure change in DA over time in DRFs. This approach proved to be a better (more sensitive) method than radiography in determining changes in DA in fractures of the distal radius.

In Paper II, a CT model was used to simulate lateral radiographic views of different radial directions in relation to the X-ray. Using an alternative reference point on the distal radius, precision and accuracy in measuring DA was increased.

Paper III and IV are based on a prospective and randomised clinical study (the GitRa trial) that compares clinical and radiographic outcomes after plaster cast removal at 10 days versus 1 month in 109 reduced DRFs. Three patients in the early mobilised group were excluded because of fracture dislocation (n=2) or a feeling of fracture instability (n=1). For the remaining patients in the early mobilised group (51/54) a limited but temporary gain in range of motion, but a slight increase in radiographic displacement were observed. Our results suggest that plaster cast removal at 10 days after reduction of DRFs is not feasible.

Paper V is based on a prospective, randomised clinical study (the GEM trial) in which 40 externally fixated DRFs were randomised to rhPDGF-BB/β-TCP into the fracture gap or to the control group. Augment® proved to be convenient and safe during follow-up (24 weeks). However, because of the nature of the study design, the effect on fracture healing could not be determined. A decrease in pin infections was seen in the Augment® group, a finding we could not explain.
To my heroes and idols:
Christina
Malin, Johanna and Oskar
This thesis is based on the following papers


II  Christersson. A., Larsson. S. Increased precision in the measurement of dorsal angulation in distal radius fractures using the dorsal-ulnar corner as the reference point versus Lister’s tubercle. *Manuscript.*


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### Abbreviations

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<tr>
<td>AC</td>
<td>Axial compression</td>
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<td>CRP</td>
<td>Central reference point</td>
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<td>CT</td>
<td>Computer tomography</td>
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<td>DA</td>
<td>Dorsal angulation</td>
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<td>DASH</td>
<td>Disability of the arm, shoulder and hand</td>
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<td>DRF</td>
<td>Distal radius fracture</td>
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<td>DRU joint</td>
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<td>EF</td>
<td>External fixation</td>
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<td>GEM</td>
<td>Name of trial on growth-factor enhanced matrix (paper V)</td>
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<td>GitRa</td>
<td>Gipstid radius. Swedish name for the trial on early mobilisation after DRF (paper III and IV)</td>
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<td>RA</td>
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<td>RSA</td>
<td>Roentgen spectrophotometric analysis</td>
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<td>TFCC</td>
<td>Triangular fibro cartilage complex</td>
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<td>VLP</td>
<td>Volar fixed-angle locking plate</td>
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Introduction

The distal radius fracture (DRF) is the most common occurring type of fracture treated in humans [1]. It is often associated with osteoporosis [2] and is therefore most common in women over 50 years of age [3]. However, it can affect all age groups, from small children to elderly people. The DRF covers a wide range of severity, from minimally displaced extra-articular fractures after low energy trauma to severely comminuted intra-articular fractures after high energy trauma. Its typical clinical feature, the dorsally displaced and angulated wrist, can be obvious and dramatic. Hippocrates believed that the pronounced malalignment was caused by a dislocation of the wrist joint [4], but in 1814 Abraham Colles understood that the condition was caused by a fracture in the distal part of the radius [5]. A DRF with dorsal displacement of the distal fragment still bears the eponym ‘Colles’ fracture’ (Figure 1).

![Figure 1. Typical bajonet shaped deformity of a Colles’ fracture.](image)

However, it was first after Lister’s work on antisepsis in 1867 and Wilhelm Roentgen’s discovery of electromagnetic radiation in 1895 that it became possible to arrive at the correct diagnosis and to treat these fractures operatively in a safe way as an alternative to conservative treatment. During the past decades, the treatment of DRFs has undergone striking change, both regarding an increase in the frequency of surgical procedures (instead of conservative treatment) as well as in open versus percutaneous methods. These changes in treatment policies are not entirely scientifically based, but rely more on a modern trend towards fixation with volar fixed-angle locking
(VPL) plates in combination with a resignation of the shortcomings of conservative treatment.

It is important that the treatment of DRFs relies on evidence-based medicine, and not on the orthopedic surgeons’ personal preferences. In addition to increased health costs, an unrestrained overuse of volar plates will lead to a decrease in knowledge and understanding of less expensive methods, such as conservative treatment and percutaneous fixations. To achieve success in conservative treatment it is mandatory to have good skills in fracture reduction and plaster cast fixation. As would be expected, the less the method is used, the inferior the outcome. During the past decades, research on DRFs has mainly focused on operative treatment, which has given added support to the use of volar plates. In the light of this trend it is even more important to focus on what benefits conservative methods can bring to modern treatment of DRFs. A long-standing problem in evaluating different treatments of DRFs has been the low precision and agreement of conventional radiography. To be able to correctly evaluate fracture displacement before and after different kinds of treatments, to find reliable connections between radiographic displacement and residual disability and to establish well-founded treatment guidelines for DRFs it is crucial to increase the accuracy and precision of radiographic measurements in DRFs.
Background

Classification of distal radius fractures

The DRF is located at the most distal end of the metaphysis of the radius, close to the wrist joint. The fracture can either be an extra-articular fracture through the metaphysis, a partial intra-articular fracture through a segment of the metaphysis, or, which is a common situation, a combination of both an intra- and extra-articular fracture. Significant efforts have been made to find a useful classification of DRFs, but it has proven to be difficult to create a classification that not only describes the spectrum of injuries but also helps in deciding the best treatment and that has a high reliability. Historical examples of classifications of DRFs, which nowadays are used less frequently, are the classifications of Gartland and Werley, Lidström, Older and Frykman. Some of these classifications have high inter-observer reliability, but the real benefit from these classifications in alerting physicians to the right treatment has been questioned. The Fernandez classification is based on the mechanism of injury causing the fracture. This classification system helps in understanding the spectrum of fractures in the distal radius, but does not help the physician in the choice of treatment.

In a scientific context the most commonly used classification is the one by the Swiss Association for the Study of Internal Fixation (ASIF/AO). This classification has an advantage in being universal for fractures in the whole body and therefore easy to understand and use for most orthopaedic surgeons. Every part of the skeleton has a unique number in the AO classification: the DRF has number 23. The fractures are divided into three groups. ‘A’ refers to an extra-articular fracture, ‘B’ to an intra-articular fracture of a segment of the metaphysis, and ‘C’ to a combination of ‘A’ and ‘B’, i.e. a fracture through the entire metaphysis and a fracture into the joint. These three groups have subgroups depending on the comminution of the fracture lines. Thus, the AO classification can describe the severity of the fracture. The reliability of the classification system is high but, unfortunately, the reliability decreases when dealing with subgroups.

The most useful classification for deciding the type of operative treatment of an intra-articular DRF is the ‘fragment specific system’ based on the work of Mellone [6] and modified by Leslie [7] (Figure 2). This system describes the major articular fragments that may occur in a DRF: the radial column, ulnar corner, dorsal wall, volar rim and free intra-articular fragments. To-
gether with the ‘three column model’ by Rikli [8], it helps in choosing approaches and implants preoperatively. Other important injuries, which are not included in the above-mentioned classifications but often co-exist with a DRF are the injuries in the distal radioulnar joint (DRU joint) or in the carpal region. Fractures at the base of the ulnar styloid process or ruptures in the triangular fibrocartilage complex (TFCC) may cause instability in the DRU joint, which has a negative effect on clinical outcome [9]. Scaphoid fractures and ligamentous injuries between the scaphoid and the lunate bone are examples of carpal injuries that can coexist with a DRF and may need treatment in addition to the DRF.

Additional to the radiographic appearance of a DRF, an analysis of the characteristics of the patient is also important when classifying and determining treatment of a DRF. The patient’s age, level of activity and bone quality are important factors in treatment decision making. So far, no classification system has successfully included these patient-related factors.

![Figure 2](image.png)

*Figure 2.* Fragment specific system; a) Radial column (styloid) b) dorsal wall c) ulnar corner d) volar rim.

**Radiographic measurements**

A DRF can displace in any direction, both in terms of angulation and sideward dislocation. However, some patterns of fracture movements are more common than others. The most common direction of displacement is dorsal angulation (DA), which gives the wrist its characteristic bayonet-shaped appearance (Figure 1). A DRF with DA bears the eponym Colle’s fracture. Two other common directions of fracture displacement are radial
angulation (RA) and axial compression (AC). All three types of malalignment can be quantified, where the magnitude of these measurements is considered to describe the severity of the DRF. In addition to angulation and compression, the distal fragment in a DRF can displace sideward, either in the frontal or in the lateral plane (or both). The main consequence of a sideward displacement is that the cortical contact between the fragments is decreased, leading to impaired stability of the fracture and increased risk of additional displacement.

On the radiographs, the comminution, both in the articular surface in an intra-articular fracture and in the main fracture gap, is visualised. DA often leads to some degree of comminution on the dorsal side of the fracture and RA often to some degree of comminution on the radial side. The more comminuted fracture, the more unstable the fracture tends to be, leading to an increased predisposition for redisplacement to its initial position, or to an even worse position than initially, after a reduction has been performed.

The literature can give the impression that the technique for measuring displacement of a DRF is well-anchored among radiologists and orthopaedic surgeons. However, articles that report results of radiographic measurements of DA, RA and AC seldom describe in detail how these measurements have been performed. At best, there are two-dimensional (2D) simplified drawings of the distal radius with lines connecting landmarks that are easy to define on the drawings (Figure 3).

*Figure 3. Schematic drawings of the measurements on radiographs of a) dorsal angulation, b) radial angulation, c) axial compression*
DA is measured on the lateral radiograph as the angle between a line connecting the most distal volar and dorsal margins of the articular surface and a line perpendicular to the long axis of the radius [10, 11] (Figure 4). The long axis of the radius is drawn through the center of the distal radius at 2 and 5 cm from the joint line [12] (Figure 15).

When measuring RA and AC, the central reference point (CRP) must be identified to avoid the possibility that the values of RA and AC are affected by the degree of DA [13]. This point lies in the sigmoid notch, midway between the volar-ulnar and dorsal-ulnar corners of the joint surface, close to the DRU joint. If the X-ray beams were parallel to the joint line, the volar-ulnar and dorsal-ulnar corners of the joint surface coincide and form the CRP. However, if the X-ray beams were not parallel to the joint line (e.g., in severely dorsally angulated fractures), the volar and dorsal margins of the articular surface diverge and the point midway between the volar-ulnar and dorsal-ulnar corners of the joint line constitutes the CRP. The CRP is the ulnar landmark of the line that represents the joint surface when measuring RA and AC [13] (Figure 5).
The radial angle is measured on the frontal view as the angle between the joint surface, from the top of the radial styloid to the CRP, and a line perpendicular to the long axis of the radius [10] (Figure 6). The AC is measured on the frontal radiograph along a line that is parallel to the long axis of the radius, as the distance between the top of the ulnar head and the CRP [14] (Figure 7). Previously, shortening of the radius was measured as the distance from the top of the radial styloid to the top of the head of the ulna along a line that is parallel to the axis of the radius, called the radial height or radial shift [10]. However, because this value is influenced not only by the shortening of the radius but also by the RA of the articular surface, this way of describing shortening of the radius is no longer being used.

Figure 5. The central reference point (red arrow) is used for measurements of radial angulation and axial compression, and is defined as the point midway between the volar and dorsal margins (black arrows) of the joint surface at the DRU-joint.
Figure 6. Measurement of radial angulation on radiograph.

Figure 7. Measurement of axial compression on radiograph.
These descriptions of radiographic measurements are easy to understand and well-established among orthopaedic surgeons. However, when looking at a real radiograph, not just a simplified drawing, the number of pitfalls is obvious. Several reference points have been identified on the volar and dorsal sides of the joint, and the size of DA depends on which reference points that are used [15]. The most commonly used reference points on the articular surface when measuring DA are the most distal volar and dorsal margins of the joint. These points are the teardrop on the volar side, located close to the DRU joint, and the Lister’s tubercle on the dorsal side, located midway between the DRU joint and the radial styloid. Only in a true lateral image of the wrist are these structures well-defined. The definition of a true lateral image is when the forearm is in neural rotation, i.e. when the volar margin of the pisiform bone lies within the middle third of the part of the scaphoid bone that protrudes volar to the capitate bone. In addition, in a lateral radiograph of the arm the X-ray beams should be tilted 15° radially for better assessment of the ulnar part of the articular surface of the radius [16-18].

A conventional radiograph is a 2D image of a three-dimensional (3D) object. This circumstance causes sources of error when characterising DRFs (e.g., when measuring an angle including the joint line). A conventional radiograph lacks depth in the picture and therefore all the contours unite into the same plane. This problem results in a blurred impression, making it difficult to distinguish all contours reproducibly, especially when consecutive images, unintentionally taken in slightly different positions, are compared. For instance, the teardrop on the volar side of the wrist joint looks different when pictured in slightly different projections.

A change in position, in supination/pronation or in radial/ulnar direction, from one image to another of the same wrist, will affect the value of DA even though no actual change in angulation has occurred [15, 17, 19]. The reason for this is that the reference points, which are used for measurements, move in relation to each other if the position of the wrist changes between two images. These movements, in turn, change the values of the angles measured on the radiographs. Because the teardrop, which is the reference point on the volar side of the joint, lies more ulnar compared with Lister’s tubercle, which is the reference point on the dorsal side of the joint, ulnar deviation of the X-ray from the desired 15° radially directed view when the picture is taken, results in a lower value for DA. Further, radial deviation of the X-ray from the desired 15° radially directed view results in a higher value for DA, just by changing the direction of the X-ray. This source of error could be avoided if reference points, which lay opposite one another (i.e. at the same distance as each other from the DRU joint) were used to create the line through the joint. In that case ulnar or radial deviation of the X-ray will not change the relationship between the volar and dorsal reference points in
the joint when looking at the wrist in the lateral view. The dorsal-ulnar corner [6, 7, 20] of the distal radius joint line lies nearly opposite to the volar teardrop. If using the dorsal-ulnar corner as the dorsal reference point, the problems with low reliability in DA measurements may be reduced (Figure 8. On the other hand, finding the dorsal-ulnar corner on the lateral projection of the distal radius is more difficult than finding Lister’s tubercle, a circumstance that can reduce the positive effects of choosing a more adequate reference point.

It has been shown that the reliability in measuring DA, RA and AC on radiographs is low and that these methods are not precise enough to make treatment decisions or evaluate outcome in DRF [21, 22]. Hitherto, measurement of radiographs in a scientific context has been investigated by comparing radiographs to radiographs, both intra- and inter-individually. In this way only the reliability and not the validity of radiography has been examined. To be able to determine whether radiography is a valid method, measurements on radiographs have to be compared with a more exact reference standard, but no such method exists. The most optimal situation would be to find a radiographic method that is valid, reliable, inexpensive and gives low radiation. This method could be used in daily practise when dealing with DRFs. The second-best situation would be to find a method that at least is valid and reliable. This method could be used as a reference standard to optimise the validity and reliability of more available methods, such as radiography. Roentgen spectrophotometric analysis (RSA) is a valid method for accurate measurements of movements between two bone segments. However, multiple metallic beads must be implanted in every bone segment. Consequently, RSA is impractical to use, especially when conservative treatment methods are examined. Computer tomography (CT) gives 3D images and therefore has the potential for accurate measurements of fracture displacements, but no methods to date based on CT have proven applicable for this purpose [23, 24].

When the two clinical studies in this dissertation (the GitRa and GEM-trial) were completed and the radiographs were to be assessed, it became evident that the precision of the radiographic measurements were unacceptably low, especially for DA. This is because the measurements proved to be highly dependent on the direction of the X-ray at the time the images were taken. We decided to develop a more precise method for measuring DA on CT in the hope that it would increase our understanding of DA measurement and on which a better method for DA measurements on radiography could be based.
Figure 8. Two lateral views of a wrist taken at the same follow-up in slightly different radial directions of the X-ray. The two upper and the two bottom images are identical. On the two images on the left, the conventional reference point, i.e. Lister’s tubercle, has been used for measuring dorsal angulation, and on the two images on the right side the dorsal-ulnar corner has been used. No actual displacement has occurred between the images. Anyway, when using Lister’s tubercle, the value of DA changes, but almost not when using the dorsal-ulnar corner.
Treatment considerations

A DRF can be described as somewhat stable. When a fracture is described as stable, it has relatively little inherent tendency for further displacement, either from its primary position or from a reduced position. The degree of fracture stability depends on several factors, including bone contact, fracture comminution, degree of displacement and bone quality.

A radiographic factor known to represent a high degree of instability of a DRF is AC [25]. Another important radiographic factor to assess the stability of a DRF is whether the volar cortex is displaced. If the volar cortex were displaced, the fracture is highly unstable. This circumstance also applies for the stability after reduction. If a displaced volar cortex were reduced, the stability is much higher compared with whether the volar cortex remains displaced [26]. Increasing age of the patient, presence of osteoporosis and dorsal comminution are other factors related to increased fracture instability in a DRF [25, 27]. When treating a DRF, the physician must assess the degree of displacement and the stability of the fracture, and then decide about reduction and what kind of additional stability the fracture needs during the healing process to avoid malunion.

The fracture stability can be increased by different treatment strategies. Conservative treatment with a plaster cast increases fracture stability only partially. It is tempting to believe that the magnitude of increased stability depends on how the plaster cast is applied. An expedient plaster cast, with three-point support to counter the dorsal bending deformity of the DRF, originally described by John Charnley [28], is considered to provide more stability to a wrist fracture than a flat splint on the dorsal side of the extremity. John Charnley stated, “…it takes a curved cast to produce a straight bone”. Although this quotation has been repeated over the years in varying settings on conservative treatment of DRF, it has never been scientifically verified.

It is well-known that a plaster cast fixation is unable to retain all the improved fracture position achieved when a DRF is reduced. It seems as though AC is the most difficult displacement to retain in a plaster cast and that the AC often returns to its initial position after conservative treatment [29-34]. DA, on the other hand, is often retained to some extent in the plaster cast; RA adopts an intermediate position between AC and DA during a tendency to return to the initial position when a DRF is treated conservatively [32, 33, 35]. The magnitude of redisplacement during conservative treatment in a plaster cast is also dependent on the age of the patient. The older the patient, the more the fracture will redisplace in a plaster cast, which is due to inferior bone quality with advanced age [29, 36-38]. There seems to be a dividing line at about 60 years of age, after which fracture instability during conservative treatment increases substantially [37, 39-41]. This means that in conservative treatment of DRFs the physician must plan for some degree of
displacement after the reduction, anticipate the final deformity and decide whether the expected final deformity is acceptable for the patient in question.

There is no well-defined consensus on what type and size of displacement that causes residual disability after the treatment of a DRF. Moreover, there is a widespread belief among orthopaedic surgeons that the final radiographic appearance of a DRF affects clinical outcome to only a limited extent. Long ago the belief was that patients with DRFs reach full recovery independent of the final radiographic deformity. Some newer studies have supported this opinion [35, 42-44]. However, this conclusion has been refuted. Today, the most established opinion is that there is a connection between the final radiographic deformity and the remaining clinical disabilities after a DRF [31, 45-49]. The fact that patients with symptomatic malunions after DRFs achieve better function after corrective osteotomies has also been taken as proof that there is a correlation between deformity and disability [50].

The radiographic parameter most associated with poor outcome after a DRF is the amount of AC. According to previous studies, a remaining AC of 2-5 mm after treatment is associated with a poorer outcome [45, 51-53]. For RA and DA, the results are inconclusive. A final DA of >15-20° or a RA < 5-15° from a line perpendicular to the long axis is likely to give an exacerbated clinical result [45, 52, 54, 55]. If different types of deformity co-exist, a smaller amount of displacement is needed for residual disability: for example, 1 mm of AC together with 10° of DA gives significantly more persistent disability compared with only compression or DA separately [48]. In addition, intra-articular incongruity of > 2 mm results in posttraumatic arthritis and poor clinical outcome in young adults [56].

The clinical effects of a malunion after a DRF have been shown to be age-dependent. The older the patient, the clinical outcome will be less affected by the persisting deformity [57-59]. Hence, the physician must take in mind that the older the patient, the more unstable the fracture, but at the same time, the more acceptable the deformity. This equation is difficult to transfer into clinical practise. In recent years it has been shown that it is not high age per se that makes residual deformity acceptable. The acceptance of deformity depends more on the preceding functionality level of the patient. A study has shown that in low-demand patients > 60-65 years of age there is no connection between radiographic and functional outcome, with functional results often good despite fracture malunion [60, 61]. A consequence of this result is that moderately displaced DRFs in low-demand patients aged 60-65 years or older can be treated conservatively, even if a perfect reduction has not been achieved or retained during the treatment. When conservative treatment was compared with volar plate fixation for moderately displaced DRFs in patients > 65 years of age, the conservatively treated group achieved significantly inferior grip strength and radiographic end result, but
all other parameters, including functional scores, did not differ between the groups [62]. It seems that malunion after a DRF leads to decreased grip strength [43] and that the need for a certain amount of grip strength can be used when differentiating low-demand from high-demand patients. Only patients that tolerate low grip strengths, independent of age, will do well despite residual deformity. A study on exclusively active and high-demand elderly patients over 60 years old showed a relationship between residual deformity and reduced functional outcome after a DRF in this group of patients. The study also showed that the radiographic limit values for avoiding permanent disability after a DRF are the same for elderly high-demand patients > 60 years as for younger adults [63]. Another factor to consider is that operative treatment in patients > 65 years results in more complications than conservative treatment [64].

Internal fixation, i.e. VLP, provides high fracture stability. However, small fracture movements can occur even when the plate is correctly applied [65]. The external fixator (EF) lies midway between internal fixation and conservative treatment in fracture stability support. An EF in a DRF most often bridges the wrist joint. During treatment, the ligaments over the wrist joint will be somewhat elongated because of the distraction forces from the fixator. This leads to some degree of fracture instability as well as subsequent small movements in the fracture. It is also known that a patient with osteoporosis, which often coexists with a DRF, will have significantly more secondary displacement in the fracture during treatment in an EF compared with a patient with normal bone quality [66]. However, EF is still significantly more stable than conservative treatment in patients with osteoporosis [67]. In conservative treatment the displacement occurs mainly during the first two weeks after plaster cast application, but in EF most of the displacement occurs later during treatment [68]. Both a plaster cast and an EF must be removed after approximately 4-6 weeks to avoid joint stiffness. Several studies show that a DRF is not completely healed and stable after 4-6 weeks [32, 69-72]. However, the late fracture movements that occurred after the removal of the plaster cast, k-wire or EF in these studies were small and most often not clinically meaningful. This means that the fracture can further displace to some degree after the plaster cast or EF has been removed. On the contrary, a VLP is only occasionally removed and only after completed fracture healing. Therefore, only a limited amount of late fracture displacement occurs after VLP.

Conservative treatment

In DRFs conservative treatment is the most commonly used treatment. Even though the proportion of operative treatment is increasing, 80% of all DRFs
are still treated conservatively. Conservative treatment in undisplaced fractures consists of plaster cast fixation *in-situ*, and in displaced fractures of closed reduction and plaster cast fixation. The conventional fixation time in a plaster cast is 4-6 weeks (Figure 9).

**Figure 9.** Traditional plaster cast fixation of a distal radius fracture. The cast covers approximately two-thirds of the circumference of the lower arm, preferably on the dorso-radial side, and extends from just below the antecubital fossa to the metacarpal-phalangeal joints.

An orthopaedic surgeon is taught to always achieve good reduction in an extra-articular fracture close to a joint. The DRF is peculiar in that the anatomy of the wrist does not have to be totally restored after a fracture to achieve acceptable function, partly because of some preexisting overcapacity in the range of motion of the wrist. Small residual deformities can still lead to full recovery.

An orthopaedic surgeon is also taught to avoid extended periods in a plaster cast. In the lower extremity plaster cast fixation is often not recommended because of long fracture healing time; in the shoulder and elbow immobilisation should be avoided because even a short time of fixation can lead to persistent stiffness of the joints. Even in this matter the DRF is peculiar in that it heals relatively fast and is not known to develop a permanently decreased range of motion in the long run even after extended times of immobilisation [73]. Not even after surgical treatment is the wrist joint sensitive to immobilisation. In a comparison between immobilisation in a plaster cast for 2 versus 6 weeks after volar plate fixation of DRFs no differences between the treatment groups in range of motion, grip strength or functional scores were seen at the 3- or 6-month follow-up [74].

There is wide agreement that minimally displaced DRFs (DA<5°) can be treated conservatively without plaster casts and still heal in the same radiographic position as with plaster cast fixation [75-77]. There are divergent opinions, however, on the functional benefits of the treatment without plaster
cast in these studies. In one study the active group had better functional result after 1 year [75]; in another study the active group had only temporary better functional results compared with conventional plaster cast fixation [77]; and in a third study no differences in functional outcome were found between the groups. In slightly more displaced fractures, some of them being reduced, 3 weeks versus 5 weeks of plaster cast fixation were compared. The findings indicated no differences in radiographic or functional outcome in two studies [78, 79], but a small increase in RA and a temporary increase in functional outcome in the early mobilised group were seen in another study [80].

Sarmiento introduced and advocated the conservative method of functional bracing of DRFs in the 1970s [81, 82], but he never evaluated the treatment in comparison with other methods. Later, one study showed that Sarmiento’s functional brace leads to a temporary better functional result compared with conventional plaster cast fixation early in the rehabilitation phase, but not to any permanent benefits over time [83]. The active group in this study displaced slightly more in RA compared with the control group. Another study comparing Sarmiento’s brace against conventional plaster cast fixation did not show any differences between the groups in functional or radiographic outcomes [84]. In the era following Sarmiento’s theories on early functional treatment numerous studies were performed comparing conventional conservative treatment of DRFs, i.e. 4-6 weeks in a plaster cast, with fixation in braces covering the lower arm down to the styloid process of the radius but without immobilising the wrist joint. Long-term advantages in functional outcome in favour of the active group treated with this kind of brace were seen only in one study, in which the range of motion, but not grip strength, was better in the active group at 6 months [85]. In the other studies only temporary functional benefits, but no long-standing positive effects, were noted in the active groups [86-88].

Sarmiento himself used a rigid brace over the dorsal aspect of the wrist that inhibited dorsal extension in the wrist joint but permitted volar flexion. It also extended proximally over the elbow - restricting rotation - but permitted elbow flexion and extension (Figure 10). The other type of brace, as mentioned above, extended down to the radial styloid, but did not pass over the wrist joint, and proximally it did not include the elbow.

All these orthoses were created to support the DRF as much as possible without preventing movements of the wrist or usage of the hand. A possible negative effect of less rigid fixation is increased fracture displacement during treatment. However, most of these studies, comparing clinical and radiographic results after different kinds of functional bracing following DRFs, have shown the same radiographic outcome compared with traditional plaster cast fixation for 4-6 weeks. These results, showing unaffected radiographic outcomes after early mobilisation in comparison with plaster cast
fixation, suggest that a preserved fracture position after a DRF depends more on the inherent stability of the fracture itself (because of interference between the fracture fragments) than on the additional stability that a plaster cast provides. Hence, the fracture position is not affected by early removal of the plaster cast. On the other hand, the fractures in these studies were mainly slightly displaced and not always reduced before fixation. Thus, these fractures had some degree of stability from the beginning. The previously mentioned study by de Bruijn showing increased RA after treatment with Sarmiento’s functional brace as compared with conventional cast fixation was made on fractures with different degrees of displacement [83]. Even fractures with severe displacements had been included. None of the other referred studies had included severely displaced fractures. The difference in radiographic outcome between the two treatment groups in de Bruijn’s study, together with the fact that also severely displaced fractures had been included in the study, implies that conventional plaster cast fixation may ultimately have a stabilising effect in some DRFs.

Operative treatment

The first surgical method described to stabilise a DRF was a percutaneous pin by Lambotte in 1908. However, it was first in the 1970s that multifocal percutaneous pinning became a common surgical method, mostly thanks to the work of Kapandji [89]. The EF of DRFs was introduced by Anderson
and O’Neil in 1944, but it was not until the 1980s that the use of EFs became widespread through Vidal’s work on ligamentotaxis [90] (Figure 11).

With the beginning in 1958, the AO group in Switzerland started to develop techniques for internal fixation of fractures in general. However, in DRFs fixation with plates and screws lacked popularity. Due to basic principles of stability, dorsally displaced DRFs needed to be stabilised with a dorsal plate; however, a plate on the dorsal side of the wrist caused a high frequency of irritations of the tendons. Therefore, EF and multifocal percutaneous pinning remained the most commonly used surgical treatments for displaced DRFs in the 1980s, 1990s and mid-2000s. After the introduction of fixed-angle locking plates on the volar side of the wrist (VLP) for dorsally displaced DRFs in 2002 [91], the use of VLP increased rapidly (Figure 12). In 2006, the VLP and the EF changed position as the most commonly used device for surgical treatment of displaced DRFs in Sweden [92]. At that time, there was only sparse scientific support for the rapid change in treatment regime from EF to VLP. The change in treatment was based more on the orthopaedic surgeon’s personal preferences. During the years that followed, only a few studies concluded that VLP, instead of percutaneous techniques, produces a better outcome [93-95]. Most of the studies comparing EF and VLP have concluded that the VLP is superior to EF in relation to clinical outcome only during the early phase of treatment, but the differences are no longer significant after 12 months [96-104]. Several meta-analyses have concluded that VLP can be advantageous in active patients who benefit...
from rapid mobilisation [105-108]. The only parameters that differ between the groups at 12 months are a statistically significant, but clinically less important, improvement in functional scores and radiographic parameters, particularly in AC (in favour of VLP versus EF). However, there is a higher frequency of reoperations in the VLP group. In recent years, in which the popularity of the VLP has continued to increase, the proportion of DRFs treated surgically has also markedly increased. In 2005, 16.0% of all DRFs in Sweden were treated surgically. In 2010, this number had increased to 20.2%, being most pronounced in females aged 50-74 years [92].

VLP leads to somewhat different complications than conservative treatment and EF. The rate of major complications after VLP, defined as tendon- or hardware-related problems leading to reoperation, nerve injuries or complex regional pain syndrome, is approximately 6-27% [109-112].

*Figure 12. Volar fixed-angle locking plating of a distal radius fracture*
Evaluation of treatment

In a historic perspective outcome after DRFs in scientific studies has been measured in terms of objective evaluation based on radiographic end result and measurements of physical capabilities. The physical evaluations have consisted of grip strength, measured by a Dynamometer (Figure 13), pinch strength, measured by a Pinch meter (Figure 14), and range of motion in the radio-carpal joint (flexion, extension, radial deviation and ulnar deviation) and in the DRU joint (supination and pronation), measured by a Goniometer. Grip strength, pinch strength and range of motion of the injured wrist are compared with the uninjured side, with differences used for comparison. The range of motion is often symmetric in persons previously uninjured in the wrists and the range of motion in the right and left wrist is therefore interchangeable. In contrast, grip strength is not symmetric. The most accepted opinion is that in right-handed persons the right hand is approximately 10% stronger than the left hand [113, 114]. However, in right-handed persons the difference in hand strength between the right and left hand decreases with increasing age [115, 116]. In left-handed persons the left hand is equally strong as the right hand [114, 117].

Figure 13. Jamar dynamometer for measurement of grip strength.
In addition to the objective evaluation, the degree of pain experienced by the patient is an important aspect when evaluating the end result after a DRF. For this purpose, different types of pain assessment scale are used: the Numeric Pain Rating Scale, Verbal Pain Intensity Scale or, most commonly, Visual Analog Scale (VAS). On a VAS, the patient marks the point that represents the amount of pain on a continuous line between two verbally presented extreme values. The position on the line is transferred to a numeric value by measuring the distance from the start of the scale. Different kinds of pain can be queried: pain at rest, pain during exercise or the average value of the pain experienced within a certain period (e.g., during the past 24 hours). Even though the VAS provides the investigator with numerical values, it is important to remember that the VAS is an ordinal and not an interval scale [118]. The VAS can be used as a separate value or as one of many items in a complex evaluation score.

In the 1980s, different rating systems were introduced, which also included the patient’s subjective experience of the end result. From this moment on, the evaluation of fracture treatment in a scientific context was based on three components: radiographic, physical and subjective evaluation. Such assessment scores, based on physical and subjective evaluation, are called functional assessment scores. The first developed functional assessment scores were primarily based on pain and objective measurements. However, it was the doctor who filled in the protocols and the scores were not tested for reliability or validity. The most commonly used early assessment score after DRFs was the Demerit point system introduced by Gartland and Wer-
ley in 1951 [119], later modified by Sarmiento [81]. Other well-known assessment instruments are the de Bruijn score [83] and the Smith and Cooney modification [120] of the Mayo wrist score [121], which, in turn, was a modification of the Green and O’Brien score [122].

The scores used today, originally developed in the 1990s, pay more attention to the patients’ subjective experience of the outcome. The newest evaluation scores are solely based on the patients’ own experience, integrating both physical and subjective evaluation by simply asking the patients questions about specific difficulties in activities of daily living or about their own experience of their summative health. This type of evaluation, called health-related quality of life (HRQoL), deals with the psychosocial consequences and functional impact of an injury. A major advantage with this design is that the evaluation can be performed without the involvement of the physician when outcome data are recorded. The protocol is filled in by the patients as patient-reported outcome measurements (PROMs) and can either be generic, i.e. focusing on general health and quality of life, or disease- or region-specific. A generic health score is preferable when different kinds of health-related problems are compared, but region-specific scores are more appropriate when evaluating different treatment options for a specific diagnosis or injury. The most well-known and commonly used generic assessment scores are the EQ5D (EuroQol) from 1990 [123] and the SF-36 (Short-Form Health Survey) from 1992 [124]. The MFA (Musculoskeletal Function Assessment) questionnaire from 1996 [125] is a region-specific evaluation scale and was originally designed to detect small differences in functioning among patients with musculoskeletal disorders in the extremities. A short version of the score (Short Musculoskeletal Function Assessment, SMFA) was developed in 1999 [126]. When evaluating DRFs, it is often preferred to use a more region-specific scale for the upper extremity or the wrist. The DASH (Disability of the Arm, Shoulder and Hand) was created in 1996 [127] as an assessment scale for injuries in the upper extremity. This tool was translated into Swedish and validated in 2000 [128]. It has been widely used for outcome measurements after DRFs, but is more appropriate for evaluating complex injuries in the upper extremity [129, 130]. The Patient-Related Wrist Evaluation (PRWE) was created in 1998 [131] as a specific evaluation scale for wrist injuries; it was translated into Swedish and validated in 2009 [132, 133]. The PRWE is the most studied and used PROM today for DRFs [134].

Fracture healing

The process of fracture healing is most often described in cortical bone and can be simplified into four stages: an initial hemorrhagic phase the first
week after the fracture, a proliferative phase the following weeks, a callus formation phase after the first month until the fracture is healed and a remodelling phase the following years [135]. In contrast, a fracture in cancellous bone heals with no or limited callus formation [136]; rather, the bone formation is mainly restricted to the fracture gap. However, the healing capacity is larger in cancellous bone than in cortical bone [137] because of the larger bone surface, better blood supply and thicker periosteum [138]. The amount of callus formation in cortical bone depends on the stability of the fracture. Some interfragmentary bone movements are needed to induce healing [139]. But then, too large interfragmentary movements may cause hypertrophic non-union [140]. The healing of metaphyseal bone also follows these biomechanical principles [141].

A fracture that is rigidly fixed, such as with a plate and screws, heals with primary bone healing. Rigid fixation of a fracture results in intramembranous ossification, i.e. the fracture heals with calcified bone without going via cartilage formation. A fracture that is not rigidly fixed, such as with a plaster cast, an external fixator or an intramedullary nail, heals with secondary bone healing. This is called endochondral ossification, which means that a fracture, because of some degree of instability, first is filled with cartilage tissue and later with calcified bone.

The fracture healing process consists of a complex range of interactions at the cellular level. Platelets, monocytes and fibroblasts release a series of growth factors that stimulate differentiation of mesenchymal-derived cells, cellular proliferation and angiogenesis. The most well-known growth factors are the bone morphogenic proteins (BMPs), the transforming growth factors (TGFs), the insulin-like growth factors (ILGFs), the platelet-derived growth factors (PDGFs) and the fibroblast growth factors (FGFs). In 1965, it was shown that demineralised bone matrix induces new bone formation [142]. The first growth factor that was isolated from bone was the BMP in 1979 [143]. Later, different subtypes of BMPs were identified and cloned [144, 145]. Several clinical studies have demonstrated the efficiency of BMPs in accelerating fracture healing [146, 147]. Historically, local administration of autogenous bone graft has been used to stimulate fracture healing, but because of donor-site complications [148] and lack of harvestable grafts in patients with osteoporosis or prior autograft surgery, a need for alternative approaches to induce fracture healing has been suggested. For clinical use, rhBMP-2 and rhBMP-7 have, until recently, been available for local administration in non-unions, bone defects and arthrodesis. Although BMP seems to be as effective as autogenous bone graft in the treatment of tibial non-unions [149], autogenous bone graft remains the gold standard in the treatment of non-unions [150].

PDGF is an early initiator of wound healing and bone generation [151]. PDGF is responsible for the early phases of the bone healing cascade and is
both a more powerful chemotactic agent and a stronger mitogen for mesenchymal stem cells compared with BMP-2 [152, 153]. This dual action in the early phase of bone healing has created expectations of PDGF being a more potent substitute to autologous bone graft than BMP-2 and BMP-7. PDGF also promotes angiogenesis [154]. PDGF is a whole family of growth factors and is only active in the form of a dimer. PDGF-BB is the only isomer that binds to all known types of PDGF receptor and has therefore been used in clinical studies. Both in vitro and in vivo preclinical studies have shown that rhPDGF-BB stimulates bone formation [155, 156]. In animal studies (rats and rabbits) rhPDGF-BB had a stimulatory effect on fracture healing [157, 158]. So far, there are few clinical studies assessing the potential stimulating effect of PDGF on bone regeneration in humans. Local application of rhPDGF-BB gave a significant gain in bone formation in advanced periodontal osseous defects [159]. In studies on foot fusions rhPDGF-BB was found to represent a safe and efficacious treatment alternative to autologous bone graft [160-162]. There are no available studies in humans in which an rhPDGF-BB-containing matrix has been used in acute fractures or non-unions. An important issue in using local administration of a growth factor in fractures, non-unions and arthrodesis is the type of biomaterial that the growth factor is mixed with. The property of this biomaterial determines the concentration and duration of the release of the growth factor. In therapeutic use recombinant human PDGF (rhPDGF-BB) is often combined with a resorbable osteoconductive scaffold, beta tricalcium phosphate (β-TCP) granules.
Aims

Paper I
To compare the reliability and agreement of a CT-based method and digitalised 2D radiographs when measuring change in DA over time in DRFs.

Paper II
To compare the precision and accuracy of DA measurements in DRFs when using the ulnar corner on the dorsal side of the joint versus the generally accepted Lister’s tubercle as the reference point.

Paper III
To compare the radiographic outcome of plaster cast removal at 10 days versus 1 month after reduction in moderately displaced DRFs.

Paper IV
To compare incidence of treatment failures and the clinical outcome of plaster cast removal at 10 days versus 1 month after reduction in moderately displaced DRFs.

Paper V
To evaluate the feasibility, safety and potential use of locally administered rhPDGF-BB/β-TCP (Augment®) in acute DRFs.
Methods

Radiographic studies
CT-based 3D measurement of DA (paper I)
In paper I images of 33 DRFs treated with external fixation were retrospec-
tively assessed. The fractures had been included in the GEM trial assessing
safety and utility of Augment® (rhPDGF-BB/β-TCP) (Paper V). The frac-
tures were examined with both radiography (XR) and CT six times at specif-
ic intervals postoperatively after closed reduction and EF. The study was
retrospective and conducted on anonymous archived images. Because the
study did not handle sensitive personal information, ethical approval was not
obtained.

DA on XR and CT were measured twice by two independent assessors.
On XR, DA was measured digitally on the lateral view using software (Web
1000, AGFA) that calculated the angle between two manually placed lines.
The first line connected the volar and dorsal margins of the joint while the
second line was perpendicular to the long axis of the radius. The reference
points on the joint line were the volar teardrop and Lister’s tubercle (Figure
15).

On CT, DA was measured with a newly developed user-guided 3D tech-
nique (Appendix 1 and 2). In this technique the joint surface was marked on
the postoperative scans (Figure 16a) through three user-defined landmarks
(Figure 16b). The joint surfaces of the scans in the same patients were semi-
automatically fitted to the first scan (Figure 16c). The long axis of the radius
was taken from a calculation of the normals (i.e. vectors perpendicular to the
bone surface) of a 2-cm long segment. The normals were gathered in a dense
ring around the shaft and a line perpendicular to the ring was used as the
long axis of the radius (Figure 16d). The DA between the joint surface and
the long axis of the radius was calculated in each scan (Figure 16e). The 3D-
CT technique required at least 2 cm of the radius proximal to the fracture.
Not all CT images in the GEM trial fulfilled this criterion. Totally, 133 ex-
aminations from 33 patients were assessable and the number of adequate
consecutive CT examinations per patient was six (n=5), five (n=8), four
(n=8), three (n=7) and two (n=5).

The first examination of each patient (for both XR and CT) was used as a
reference and the following examinations in every patient were compared
Figure 15. DA on XR was measured on the lateral view of the wrist. A line was drawn between the most distal volar and dorsal margins of the joint of the distal radius (a). A second line was drawn along the longitudinal axis of the radius through the centre of the distal radius at 2 and 5 cm from the joint line (b). DA was calculated as the angle between the line through the joint (a) and a line (c) perpendicular to the longitudinal axix of the radius (b). Volar angulation in relation to the perpendicular line was marked with negative values and dorsal angulation in relation to the perpendicular line (as in the image above) was marked with positive values.

with this reference. In total, 133 examinations in 33 patients gave 100 changes in DA from one reference value to the corresponding follow-up.

Two assessors (author AC and JN) performed the evaluations on all the XR and CT images independently. Further, all measurements were repeated one more time on the same XR and CT images independently by the two assessors. The intra- and inter-observer agreement within XR and CT and between XR and CT were calculated using Bland Altman plots [163]. The measurements were represented on graphs by assigning the means of two measurements on the x-axes and the differences between the two measurements on the y-axes. In each of these analyses the mean difference and the limits of agreement (±2SD) were calculated and marked on the graphs. A value close to zero for the mean difference implies similar validity for the two methods of measurement. The limits of agreement imply that 95% of the
differences in measurements between the two methods will be within these limits. Whether a limit of agreement is acceptable has to be based on a clinical judgement of the actual size of the fracture movements. If the limits of agreement are considered acceptable, then the two methods are exchangeable. In this study we used XR as the existing reference method for measuring change in DA over time in DRFs while the new CT-based method was applied as the method to be evaluated.

**Figure 16.** Overview of the three-dimensional angle measurement technique
An alternative reference point for DA measurements (paper II)
The official instructions for taking a true lateral view of the wrist is to aim the X-ray exactly perpendicular to the frontal view. Considerable efforts are made to avoid incorrect positioning in rotation of the wrist. The ulnar edge of the hand should lie on the examining table with the radial side of the hand facing up. In this way, the lower arm lays parallel to the cassette, with the wrist imaged perpendicular to the long axis of the radius [164]. However, it is sometimes recommended to tilt the X-ray 10° radially (Figure 17) to gain a better view of the joint surface [165]. When the precision and accuracy of dorsal angular measurements on lateral views has been studied more closely, comparing DA in different radial directions, the results are consistent: a lateral view of the wrist should be taken with the X-ray directed 15° radially because of the anatomic radial inclination in a non-displaced DRF [16-18] (Figure 17). However, this knowledge has not had full impact in the instructions to the radiographic staffs.

![Figure 17. Direction of the X-ray in relation to the wrist in lateral radiographic projection. a) Perpendicular to the long axis of the radius. b) 15° radial direction of the X-ray in relation to the perpendicular line.](image)

In paper II, archived CTs of six healed DRFs in patients with a mean age of 63 years (range 59-74) from the GEM trial were retrospectively examined. The fractures had been treated with closed reduction and EF, healing in a near-anatomic position. The study was retrospective and conducted on anon-
The study did not deal with sensitive personal information and therefore ethical approval was not required.

The CT images were presented in 3D mode and made transparent, making them appear as 2D radiographies. The 3D images were rotated in the horizontal plane until the radius and ulna were projected on top of each other and thus looking like a lateral radiographic projection. The images were gradually radially directed in seven angles from a line perpendicular to the long axis of the radius to 20° radially in relation to the perpendicular line of the radius: 0°, 4°, 7°, 10°, 13°, 17°, and 20° (Figure 18). The range from 0° to 20° was used in that it covers the different directions mentioned in the literature and we therefore anticipated that it represents the majority of directions taken in clinical everyday practise.

The joint line was defined either as a line between the volar teardrop and the most distal edge on the dorsal side of the joint surface, which is usually represented by Lister’s tubercle, or as a line between the volar teardrop and the second most distal edge on the dorsal side of the joint surface (Figure 19 and 20). This reference point is usually represented by the dorsal-ulnar corner of the joint [6, 7, 20]. The same perpendicular line to the long axis of the radius was used for both measurements. The two angles were measured in all seven positions of radial directions in each of the six patients. Positive values were used for dorsal angulation and negative values for volar angulation in relation to a line perpendicular to the long axis of the radius.

The results from measuring DA from seven positions of the wrist using two reference points on the dorsal side of the joint are presented in graphs. The individual results for each patient and the mean result for all fractures

**Figure 18.** The CT images of the wrists were gradually radially directed so that it looked like they had been imaged in seven different radial directions, from 0° to 20° in relation to a line perpendicular to the long axis of the radius.
are presented in separate graphs. In each graph one line is drawn to connect the measurements using the conventional reference point, i.e. Lister’s tubercle (L) and the alternative reference point at the dorsal-ulnar corner close to the distal radio-ulnar joint (U) are marked.

Figure 19. Three-dimensional computed tomography image of the distal radius from the volar side. The volar teardrop (V) is marked on the volar side of the joint. On the dorsal side, the conventional reference point at Lister’s tubercle (L) and the alternative reference point at the dorsal-ulnar corner close to the distal radio-ulnar joint (U) are marked.
Clinical studies

The GitRa trial (paper III and IV)

In the GitRa trial (paper III and IV) consecutive DRFs with a moderate displacement, defined as DA of 5-40° and AC of 4 mm or less, treated with
closed reduction and plaster cast fixation at the emergency department at Uppsala University Hospital between September 2002 and December 2008, were screened for inclusion. The study was approved by the Ethical Committee of Uppsala University and informed consent was obtained from all patients according to the ethical guidelines of the Helsinki Declaration.

In all, 109 patients met the inclusion and exclusion criteria (Table 1). These patients were randomised at the follow-up at 10 days (range 8-13 days) after the reduction to either removal of the plaster cast (active group, n=54) or to continued fixation in a plaster cast for another 3 weeks (control group, n=55) (Figure 21). Three patients fulfilled the inclusion criteria, but declined to participate before the randomisation.

The patients who were treated with removal of the plaster cast at the 10-day follow-up after reduction received an elastic bandage around their wrist, then instructed to move their wrist freely to the best of their ability, but to avoid painful activity and heavy weight lifting. At 1 month, a physiotherapist, not involved in the study, gave identical instructions to the active and control groups about rehabilitation.

Table 1. Inclusion and exclusion criteria in the GitRa trial.

<table>
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<th>INCLUSION CRITERIA</th>
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<tr>
<td>DRF treated with closed reduction and plaster cast fixation</td>
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<td>Initial dorsal angulation 5-40°</td>
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<tr>
<td>Initial axial compression ≤ 4mm</td>
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<tr>
<td>Intra-articular step-off ≤ 1 mm</td>
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<td>Age ≥ 50 years</td>
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<td>Low energy trauma</td>
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<td>Closed fracture</td>
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<td>Reduction within 3 days after injury</td>
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<td>Intact distal ulna (except for the styloid process of the ulna)</td>
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<th>EXCLUSION CRITERIA</th>
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<tr>
<td>Previously injured ipsilateral or contralateral wrist</td>
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<td>Dementia</td>
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<td>Inflammatory joint disorder</td>
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<tr>
<td>Dorsal angulation &gt; 25° at the 10-day follow-up</td>
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<tr>
<td>Axial compression &gt; 4 mm at the 10-day follow-up</td>
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All fractures were prospectively followed at 1 (range 4-5 weeks) and 12 (range 11.5-12.5) months after reduction with X-rays, and at 1, 4 (range 3.5-4.5 months) and 12 months after reduction with clinical evaluations by a research physiotherapist (Table 2). The clinical assessments at the follow-
ups consisted of grip and pinch strength, range of motion and pain (VAS). The presence of adverse events and treatment failures were registered at all follow-ups. Treatment failure was defined during the first month as problems leading to abandonment of the given treatment and after the first month as poor outcome leading to surgical treatment of a malunited fracture. At 1 month, X-ray and clinical examinations were also performed on the uninjured wrist.

<table>
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<tr>
<th>Acute wrist fractures</th>
<th>Reduction and plaster cast fixation</th>
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<tr>
<td></td>
<td>Follow-up at 10 days</td>
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<td>Randomisation (n=109)</td>
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<td></td>
<td>removal of plaster cast</td>
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<td>(n=54)</td>
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<td>continued plaster cast</td>
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<td>follow-up at 1 month</td>
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<td>follow-up at 12 months</td>
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<td>(n=51)</td>
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Figure 21. Flow chart in the GitRa trial.

The radiographs were measured for DA, RA and AC by one of the authors (AC). Changes in displacements from admission to 12 months and from 10 days to 1 month were compared between the active and control groups.
A Jamar dynamometer was applied to assess grip strength in the hand and a pinch meter for pinch strength in the pinch grip. The patients performed three consecutive compressions with the Jamar dynamometer and the pinch meter at each follow-up: the third compression should not be the highest. If the third compression was the highest, a fourth compression was performed and the first compression was omitted, and so on, until the last compression was not the highest. The average value of the three compressions for each instrument was recorded. Since the 10% rule for grip strength has been questioned [115, 116, 166], the differences in hand strength between the groups were calculated both with and without using the 10% rule. A goniometer was used to measure the range of motion in the wrist (flexion, extension, supination and pronation). Differences in grip- and pinch strength and range of motion, between the injured and uninjured side were calculated at each follow-up.

Pain was assessed using a VAS scale from 0 (no pain)-10 (intolerable pain). At each follow-up, the patients were told to set the VAS scale on a level that represented the average pain experienced during the past 24 hours. The values were expressed with one decimal place. At the follow-ups, the question about pain was asked before plaster cast removal in both groups to avoid the possibility of registering additional pain immediately after cast removal. At 12 months, three evaluation scores were used: the de Bruijn Score, modified by Christersson & Sanden (Figure 22), the Mayo Wrist Score, modified by Smith & Cooney (Figure 23), and the Demerit point system of Gartland and Werley, modified by Sarmiento and by Christersson & Sanden (Figure 24).

The power calculation was based on the change in DA from admission to 12 months. We assumed that the standard deviation for the change in DA from admission to 12 months was 10°. The study was powered to detect a difference between the groups of 5°, which is our estimation of a clinically relevant difference between the groups. For a 5% significance level and a power of 80%, a sample size of 63 patients in each group was needed.

For baseline characteristics, student’s t-test was used when comparing means and Fisher’s exact test when comparing proportions. Concerning the results in radiographic measurements, grip strength, pinch strength, range of motion, and physician-based scoring systems, means with 95% confidence intervals (CIs) were used for presentations in graphs or tables, and Student’s t-test was conducted to determine differences at the follow-ups. All these parameters were normally distributed, as seen on histograms and in the Shapiro-Wilk W test for normality (>0.95). The measurements of pain were not normally distributed and therefore compared using the Mann-Whitney U test, as well as graphically presented with medians and 25th and 75th percentiles. P-values < 0.05 were considered significant. The Bonferroni method was used to adjust for multiple comparisons.
Table 2. Follow-up assessments in the GitRa trial

<table>
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<tr>
<th></th>
<th>Radio-</th>
<th>Range of motion</th>
<th>Grip strength</th>
<th>Pain (VAS)</th>
<th>Functional scores</th>
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<td>Acute</td>
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<tr>
<td>Post reduction</td>
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</tr>
<tr>
<td>10 days</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>4 months</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
Figure 22. de Bruijn scoring system for functional treatment of Colles fractures [83]. Modified by Christersson & Sandén 2003: two points for ulnar deviation and two points for radial deviation have been replaced by eight points for pinch strength. Highest possible score has increased from 158 to 162 points.

### Complaints

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. pain while resting</td>
<td>10</td>
</tr>
<tr>
<td>b. pain while moving</td>
<td>8</td>
</tr>
<tr>
<td>c. pain during heavy work/excessive motion (if b=0)</td>
<td>4</td>
</tr>
<tr>
<td>d. numbness or paresthesia in the fingers</td>
<td>3</td>
</tr>
<tr>
<td>e. restricted basic daily life activities</td>
<td>10</td>
</tr>
<tr>
<td>f. pain while wringing out clothes (if b+c=0)</td>
<td>3</td>
</tr>
<tr>
<td>g. loss of power</td>
<td>3</td>
</tr>
<tr>
<td>h. subjective judgement of the end result</td>
<td>5 or 10</td>
</tr>
<tr>
<td>i. open question for complaints (if a+b+c+h=0)</td>
<td>1 or 2 or 3</td>
</tr>
</tbody>
</table>

### Motion in the wrist region

<table>
<thead>
<tr>
<th>Motion</th>
<th>0-40%</th>
<th>40-60%</th>
<th>60-80%</th>
<th>80-90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>dorsal flexion</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>volar flexion</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>pronation</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>supination</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

### Motor functions of the hand

<table>
<thead>
<tr>
<th>Motor</th>
<th>0-40%</th>
<th>40-60%</th>
<th>60-80%</th>
<th>80-90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>dynamometer</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>pinch meter</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>making a fist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>finger extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>opposition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>opening a door</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>weight lifting</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>picking up a pen</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>crumpling a piece of paper</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lifting a cup and saucer</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Signs and symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>swelling of hand/fingers</td>
<td>5</td>
</tr>
<tr>
<td>skin atrophy/hyperaesthesia/hyperhidrosis</td>
<td>4</td>
</tr>
<tr>
<td>ulnar compression pain</td>
<td>2</td>
</tr>
<tr>
<td>abnormal colour</td>
<td>2</td>
</tr>
</tbody>
</table>

### Cosmetics

<table>
<thead>
<tr>
<th>Cosmetic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>cosmetic appearance</td>
<td>2 or 3 or 5</td>
</tr>
</tbody>
</table>
Figure 23. Modified Mayo Wrist Scoring Chart (Smith and Cooney) [120]

<table>
<thead>
<tr>
<th>Score</th>
<th>Pain (25 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No pain</td>
</tr>
<tr>
<td></td>
<td>Mild pain during vigorous activities</td>
</tr>
<tr>
<td></td>
<td>Pain only during weather changes</td>
</tr>
<tr>
<td></td>
<td>Moderate pain during vigorous activities</td>
</tr>
<tr>
<td></td>
<td>Mild pain during activities of daily living</td>
</tr>
<tr>
<td></td>
<td>Moderate pain during activities of daily living</td>
</tr>
<tr>
<td></td>
<td>Pain at rest</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Satisfaction (25 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very satisfied</td>
</tr>
<tr>
<td></td>
<td>Moderately satisfied</td>
</tr>
<tr>
<td></td>
<td>Not satisfied, but working</td>
</tr>
<tr>
<td></td>
<td>Not satisfied, unable to work</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Range of motion (25 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage of normal</td>
</tr>
<tr>
<td></td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>75-99%</td>
</tr>
<tr>
<td></td>
<td>50-74%</td>
</tr>
<tr>
<td></td>
<td>25-49%</td>
</tr>
<tr>
<td></td>
<td>0-24%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Grip strength (25 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage of normal</td>
</tr>
<tr>
<td></td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>75-99%</td>
</tr>
<tr>
<td></td>
<td>50-74%</td>
</tr>
<tr>
<td></td>
<td>25-49%</td>
</tr>
<tr>
<td></td>
<td>0-24%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Final result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Points</td>
</tr>
<tr>
<td></td>
<td>Excellent</td>
</tr>
<tr>
<td></td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
</tr>
</tbody>
</table>
Figure 24. Modified Gartland and Werley Demerit wrist point system (Sarmiento) [81]. Modified by Christersson & Sandén 2003: three points for ulnar deviation and one point for radial deviation have been removed. Highest possible score has thereby decreased from 39 to 35 points.

**Residual deformity** (range, 0-3 points)  
Prominent ulnar styloid                  1  
Residual dorsal tilt                  2  
Radial deviation of hand                 2-3  

**Subjective evaluation** (range, 0-6 points)  
Excellent    no pain, disability or limitation of motion            0  
Good         occasional pain, slight limitation of motion, and no disability                   2  
Fair            occasional pain, some limitation of motion, feeling of weakness in wrist, no particular disability if careful, activities slightly restricted    4  
Poor          pain, limitation of motion, disability and activities are markedly restricted          6  

**Objective evaluation** (range, 0-5 points)  
Dorsiflexion        <45º                 5  
Supination          <50º                  2  
Palmar flexion    <30º                  1  
Circumduction                                1  
Pain in the distal radioulnar joint                 1  
Grip strength ≤60%                           1  
Pronation            <50º                 2  

**Complication** (range, 0-5 points)  
Arthritic change  
Minimum                             1  
Minimum with pain                          3  
Moderate                             2  
Moderate with pain                          4  
Severe                             3  
Severe with pain                          5  
Nerve complications (median)                                      1-3  
Poor finger function due to cast                                      1-2  

**Final results** (range of points)  
Excellent                            0-2  
Good                            3-8  
Fair                           9-20  
Poor                           ≥21
The GEM-trial (paper V)

Forty consecutive patients with a displaced unstable DRF at the Department of Orthopedics, Uppsala University Hospital were included between October 2005 and December 2007 (Table 3). The study was approved by the Ethical Committee of Uppsala University and all patients gave written informed consent before entering the study according to the ethical guidelines of the Helsinki Declaration. Each patient underwent surgical treatment that included closed reduction and a bridging EF with Hoffman compact II external fixation system. The patients were then randomised in the operating room. The two treatment groups included one group where, in addition to closed reduction and EF, Augment® (rhPDGF-BB/β-TCP) was applied locally into the fracture void (n=20) through a short dorsal incision. The controls were treated with EF alone (n=20). In the Augment® group the first 10 patients were treated with Augment® Bone Graft, whereas the last 10 patients were treated with Augment® Injectable. Augment® Bone Graft and Augment® Injectable are two separate formulations that combine rhPDGF-BB (0.3 mg/ml) with a synthetic bone matrix consisting of β-tricalcium phosphate (β-TCP). Augment® Injectable also contains soluble Type I collagen (Kensey Nash Corp.; Exton, PA), which makes it injectable through a cannula. In the Augment® group a one centimeter dorsal incision over the fracture site was made. Using an elevator, the cancellous bone inside the fracture void was slightly impacted to allow for insertion of 5 ml of Augment® Bone Graft in the fracture void in the first cohort or 3 ml of Augment® Injectable in the last cohort. In both groups the amount of rhPDGF-BB delivered to each patient was 0.3 mg. In both treatment groups pin sites were covered with sterile gauze that was changed twice a week. All EFs were removed after 6 weeks (Figure 25).

Radiographs were taken postoperatively and at 1-, 3-, 6-, 12- and 24-week follow-ups. The patient met a physician (one of the authors) at all these follow-ups in order to detect possible complications, including assessment of pin sites, redness and swelling. A pin infection was defined as redness and swelling around a pin that required treatment with antibiotics [167]. A research physiotherapist measured grip strength, range of motion (ROM), DASH scores and pain (VAS scale) according to a specific protocol on all visits. Because of the EF, the only range of motions that were possible to measure at 1 and 3 weeks were supination and pronation. At 6, 12 and 24 weeks, flexion, extension and radial- and ulnar deviation were also measured. Grip strength was measured using a Jamar Dynamometer and active range of motion was measured using a goniometer. Differences in range of motion and grip strength between the injured and uninjured side were calculated at each follow-up. At 3 weeks, X-ray and clinical evaluation were also performed on the uninjured side. Bone mineral density (BMD) was meas-
ured in the uninjured wrist within 4 weeks. Fracture healing was assessed at 6, 12 and 24 weeks by an independent radiologist (Table 4). A fracture was defined as healed when three cortices were bridged by bone.

Table 3 Inclusion and exclusion criteria in the GEM trial.

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable distal radius fracture unsuitable for conservative treatment</td>
</tr>
<tr>
<td>Low energy trauma</td>
</tr>
<tr>
<td>Closed fracture</td>
</tr>
<tr>
<td>Age ≥ 50 years</td>
</tr>
<tr>
<td>Intact distal ulna (except for the styloid process of the ulna)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EXCLUSION CRITERIA:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral fractures</td>
</tr>
<tr>
<td>Intra-articular displacement</td>
</tr>
<tr>
<td>Fractures involving the shaft of the radius</td>
</tr>
<tr>
<td>Previously injuries of the ipsilateral or contralateral wrist</td>
</tr>
<tr>
<td>Soft tissue infection at the operative site</td>
</tr>
<tr>
<td>Patients undergoing radio- or chemotherapy</td>
</tr>
<tr>
<td>Patients with a metabolic disorder or chronic medication known to adversely affect the skeleton</td>
</tr>
<tr>
<td>Physically or mentally compromised patients</td>
</tr>
</tbody>
</table>

The clinical and radiographic comparisons between the active and control group at all follow-ups were primarily made to detect any kind of complication or problem related to Augment® (rhPDGF-BB/β-TCP), which was injected into the fracture gap in the active group. For the same reason, a thorough search for complications, or any other abnormal findings, was conducted at all follow-ups. The study was sponsored by BioMimetical Therapeutics Inc. and all data were entered in digital case report forms (CRFs) supervised by a monitor ensuring complete documentation of device-related anticipated and unanticipated adverse events. The monitor performed on-site monitoring at specific intervals to verify adherence to the protocol.

The amount of redisplacement in DA, RA and AC from postop to 24 weeks, assessed by two of the authors (AC and BS), was used as an indirect sign of fracture healing. Although the study had both an active and a control group, the study was primarily not designed (powered) to detect a potential benefit in clinical or radiographic results for the active group. However, a post hoc power analysis was carried out. With the present number of patients in each group (n1= n2 = 20) and with the observed standard deviation, a difference in DA of 4°, RA of 3° and AC of 1 mm between the groups from postop to 24 weeks could have been detected with β=0.80 and α=0.05.
For baseline characteristics, student’s t-test was used when comparing means and Fisher’s exact test when comparing proportions. For the results in radiographic measurements, grip strength and range of motion, means with 95% CIs were used for presentations in graphs and Student’s t-test was conducted to determine differences at the follow-ups. All these parameters were normally distributed, as seen on histograms and in the Shapiro-Wilk W test for normality (>0.95). The measurements of pain, DASH, Augment® leakage and number of healed cortices were not normally distributed and therefore compared using the Mann-Whitney U test and graphically presented with medians and 25th and 75th percentiles. Fisher’s exact test was used for comparison of proportions in baseline characteristics and complications. P-values < 0.05 were considered to indicate a significant difference. The Bonferroni procedure was performed to correct for multiple comparisons.

Figure 25. Flow chart in the GEM trial.
### Table 4. Follow-up assessments in the GEM trial

<table>
<thead>
<tr>
<th></th>
<th>Radiography</th>
<th>Fracture healing</th>
<th>Densitometry</th>
<th>Range of motion</th>
<th>Grip strength</th>
<th>Pain (VAS)</th>
<th>DASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postop</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week</td>
<td>x</td>
<td></td>
<td>x^a</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>3 weeks</td>
<td>x x</td>
<td></td>
<td>x^a</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>x x x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>x x</td>
<td>x</td>
</tr>
<tr>
<td>12 weeks</td>
<td>x x</td>
<td></td>
<td></td>
<td></td>
<td>x x</td>
<td>x x</td>
<td>x x</td>
</tr>
<tr>
<td>24 weeks</td>
<td>x x</td>
<td></td>
<td></td>
<td></td>
<td>x x</td>
<td>x x x</td>
<td>x x</td>
</tr>
</tbody>
</table>

^a Due to fixation in EF, only supination and pronation could be measured at 1 and 3 weeks.
Results and discussion

Radiographic studies

CT-based 3D measurement of DA (paper I)

For XR, the intra-observer precision for the first assessor was 0.0 ± 4.4° (Figure 26 a) and the inter-observer precision on the first trial was -0.2 ± 4.6° (Figure 26 b). For the CT-based method, the corresponding intra- and inter-observer precision was 0.1 ± 2.0° (Figure 27 a) and 0.1 ± 1.8° (Figure 27 b), respectively, indicating that the CT-based method is more robust and repeatable than XR. Assessment of intra-observer precision for the second assessor and inter-observer agreement on the second trial revealed similar results (0.0 ± 4.0° and -0.1 ± 4.4° for XR and -0.1 ± 1.4° and -0.2 ± 2.5° for CT).

The intra-observer agreement between XR and CT for the first assessor on the first trial was -0.4 ± 7.1° (Figure 28 a); for the second assessor on the first trial the intra-observer agreement between XR and CT was -0.2 ± 6.7° (Figure 28 b). Thus, similar results were observed between the two assessors. Assessment of intra-observer agreement between XR and CT for both assessors on the second trial revealed approximately the same mean differences and limits of agreement as for the first trial (-0.3 ± 6.8° for the first assessor and -0.3 ± 6.7° for the second assessor).

The purpose of this study was to determine whether a CT-based 3D method has the potential properties of serving as a reference standard for measuring change in DA over time in DRFs. The first requisite of the CT method is that it has the same validity as XR. The second requisite is that the reliability and agreement is higher for CT than for XR. Figures 28 a and b show that the mean difference between CT and XR is close to zero (-0.4° to -0.2 °). This minuscule difference entails that the validity for the CT method used in this study was approximately the same as for XR. However, it must be recalled that it is the change in DA, not the value of the absolute DA, that has the same validity for both methods. One limitation of the study is that the CT imaging technique does not use the same landmarks as XR on the joint surface. On the other hand, a strength of the CT method is that it uses landmarks in 3D, thereby increasing the precision and accuracy of the measurements. In CT three defined points in a triangle are used to define the joint surface, whereas in XR only two points are used. This means that the abso
Figure 26. a) Intra-observer measurements for assessor 1 on XR, b) Inter-observer measurements between assessor 1 and 2 on XR. Mean difference and limits of agreement (± 2 SD) are marked.
Figure 27. a) Intra-observer measurements for assessor 1 on CT, b) Inter-observer measurements between assessor 1 and 2 on CT. Mean difference and limits of agreement (± 2 SD) are marked.
Figure 28. a) Intra-observer measurements between XR and CT for assessor 1, b) Intra-observer measurements between XR and CT for assessor 2. Mean difference and limits of agreement (± 2 SD) are marked.
lute value of the DA in a wrist will not be the same for the two methods, but the difference between two measurements for the two methods will be the same, at least if the validities are comparable, which seems to be the case for the two methods used in this study.

The limits of agreement for XR within and between the assessors are ± 4.4°-4.6° (Figure 26 a-b) and for CT ± 1.8°-2.0° (Figure 27 a-b). Accordingly, the precision of CT is considerably higher than the precision of XR. The margin of error of ± 4.4°-4.6° in XR is unacceptably high in a scientific context, and probably also in a clinical context. In contrast, a margin of error of ± 1.8°-2.0° for the CT method is more acceptable, both clinically and scientifically. In this respect, the CT method is a better choice than XR for reliability and agreement when measuring change in DA over time in DRFs. It is also possible to use CT for precise absolute measurements of DA, but before meaningful measurements can be taken from CT, the reference values for the anatomic position of the distal radius and angular limits for choosing different treatments need to be adjusted from XR values to CT values.

The primary reason for the new CT technique being more precise than XR is that it is semi-automatic and does not require the user to manually mark landmarks and reference lines on each image. Another advantage is that the CT images can be rotated to an optimal lateral projection for placing the landmarks. In contrast, XR is taken in a fixed position that cannot be changed, making it more difficult to find the same reproducible landmarks for radiographic measurements on consecutive images in the same patient.

The limits of agreement for XR compared with CT were ± 6.7° and ± 7.1° for the two assessors, respectively (Figure 28 a-b). These limits of agreement for XR against CT are somewhat larger than expected based on the reliabilities of XR and CT. This finding can be explained by an interaction effect between patient and method [168]. This interaction effect is a method error acting at the patient level. It is thus constant across all measurements on the same patient as opposed to the pure method error that varies over measurements. Therefore, the interaction effect does not influence differences between two measurements of the same method, but it does affect differences between the methods. This source of error mainly applies to XR and is caused by XR being a 2D projection of a 3D structure. Despite the use of strictly standardised protocols, XR images are taken at slightly different angles at different time points. The value of change in DA will thus be affected not only by the true change in DA due to actual fracture movement but also by a false change in DA due to the different position of the wrist when the pictures are acquired. As CT images are 3D, no such confounding effect exists with the new CT-based method.

The change in DA, as measured on XR, when the inclination of the X-ray is changed is caused by the fact that the two reference points on the joint surface are located at different distances from the DRU joint. A change in
radial direction of the X-ray when the image is taken will change the relation in height between the reference points and thereby also change the DA although no actual fracture movement has occurred. To minimise the method and interaction effect on XR, reference points on the joint surface at equal distances from the DRU joint need to be chosen.

The fractures in this study were fixed using EF and all XR and CT images were acquired postoperatively within the first 6 months. EF involves a semi-rigid device that deforms very little during treatment. The small changes in fracture position due to the stable EF during the time of fracture healing are a limitation of the study. Therefore, the values are gathered in the middle of the plots. If the Bland–Altman plots had been asymmetric, we might expect the limits of agreement to change when the change in DA increases or decreases outside the actual plot. Because all the Bland-Altman plots in the study have a square or rectangular shape, it is more likely that the limits of agreement is the same for higher and lower values than those values assessed in the study. However, it is not possible to extrapolate our results and form assumptions about the limits of agreement for more extreme values.

A disadvantage of the new CT technique is that it exposes the patients to more radiation compared with XR. However, the distal location of the wrist from the torso significantly decreases the effective dose compared with, for example, a CT of the shoulder. Further, the total dose from a CT scan of the wrist is only one-hundredth of the total background radiation for 1 year. In the future, the radiation dose can be considerably reduced if cone beam CTs (i.e. CTs with divergent X-ray beams, forming a cone) are used instead of regular CTs. In addition, when taking a radiographic image of a wrist, it is often necessary to take more than one frontal and one lateral projection, which can be caused by a need for additional views or incorrectly taken images.

The new CT-based method is not primarily intended for use in daily practise in the care of DRFs. However, it can serve as a reliable reference standard in future attempts to improve the precision of radiography. It can also be used for precise assessment of the radiographic outcome when comparing different treatment methods.

In conclusion, the semi-automatic CT-based 3D technique for the measurement of changes in DA in DRFs has the same validity as 2D radiography, but substantially higher reliability. Thus, it can be used as a reference standard when more precise measurements are required.

An alternative reference point for DA measurements (paper II)

DA values, measured by using Lister’s tubercle and the dorsal-ulnar corner in seven radial directions of the wrist from 0° to 20° in relation to a line perpendicular to the long axis of the radius, have been presented in separate
graphs for each patient (Figure 29). In all graphs there is a recurrent pattern showing a large increase in the measurements of DA based on Lister’s tubercle when the wrists are angulated from 0° to 20°, but a small decrease when the measurements are based on the dorsal-ulnar corner.

For the standard method of measuring DA using the most distal edge on the dorsal side of the joint, i.e. Lister’s tubercle, angulation increased on an average of 9.3° (range 6-16°) when the wrists were assessed in gradually increasing proximal directions in the six patients (Figure 30). When using the alternative method, i.e. the dorsal-ulnar corner of the joint as the reference point, there was a corresponding average decrease of 1.4° (range (-1) - 4°).

In radiographs taken at approximately 15° of proximal radial direction of the wrists the two reference points on the dorsal side of the joint surface converged. Therefore, the measured DA when positioning the X-ray at 15° of radial direction had the same magnitude for both ways of measuring. This conformity is represented by the intersections of the lines in the graphs (Figure 29). The graphs show that in radiographs taken in an angle between 0° and 15° of radial direction to the joint surface, Lister’s tubercle protrudes more distally than the dorsal-ulnar corner, which gives a lower value for DA compared with when the dorsal-ulnar corner is used for measurements. If the radiographs were taken in an angle that exceeds 15° of radial direction, the reference points change places: Lister’s tubercle will be located more proximally than the dorsal-ulnar corner, which gives a higher value of DA compared with when the dorsal-ulnar corner is used for measurements.

This study is consistent with previous work [21, 22] in showing that the precision of the standard method of measuring DA on radiographs in DRFs is low. This measuring problem is caused by the fact that different positions of the X-ray in relation to the wrist will result in different values of DA. Figure 30 shows that the values of DA increase approximately 9° if the position of the X-ray were changed from 0° to 20° of radial direction in relation to the wrist when Lister’s tubercle is used as the reference point on the dorsal side of the joint. However, the real DAs in the wrists have not changed, only the appeared angles. Because malpositioning of the wrist is common during radiography (which is due to practical issues and unknown fracture dislocations), the reality in both a clinical and scientific context is that the precision of DA measurements on radiographs is low. A difference of approximately 20° in the direction of the X-ray in consecutive images is consistent with how it is in reality. Thus, low precision would be expected [18, 164, 165]. The solution to this problem might be to develop a more rigorous protocol for taking radiographs of the distal radius. Such rigor would probably increase the precision, at least temporarily, before tiredness to strict routines would lead to decreased compliance among the staffs. It will also remain impossible to foresee the actual fracture dislocation in the fracture of the X-ray in relation to the wrist would not lead to a correct image.
Figure 29. Dorsal angulation on radiographs of the wrist at different radial directions of the X-ray in six patients.
Figure 30. Dorsal angulation on radiographs at different radial directions of the X-ray. Mean values for the six patients in Figure 29.

Therefore, the only definite solution to this problem is to find landmarks on the radius not affected by a change in the position of the wrist while the image is being taken. The central issue is to find landmarks on the volar and dorsal side of the joint surface that are located opposite to each other, i.e. at the same distance from the DRU joint. In this way the relationship between the landmarks would not change between different radial directions of the X-ray when the pictures are taken.

The study demonstrates that the precision of DA on radiographs is low with Lister’s tubercle as the reference point. It also shows that the precision can be increased by changing the reference point on the dorsal side of the joint to the dorsal-ulnar corner. When looking at the distal joint surface of the radius, it becomes apparent that the dorsal-ulnar corner is not located exactly opposite to the volar teardrop, but slightly ulnar (Figure 31). This relation explains why the measured angle, when using the dorsal-ulnar corner, slightly decreases with a concomitant increase in radial direction of the X-ray. Thus, the dorsal-ulnar corner is not a perfect choice. However, there are no well-defined structures on the volar and dorsal side of the distal radius joint surface that are located exactly opposite each other.
Figure 31. The joint surface of the distal radius: Lister’s tubercle (L), the dorsal-ulnar corner (U) and the volar teardrop (V). The red lines represent the direction of the X-ray beam in a lateral view. The blue lines are placed perpendicular to the beam. Reference points along the same blue line are located opposite each other when viewing the wrist in a lateral projection. Reference points along the same blue line are the optimal location for the measurement points, which makes DA unaffected by the amount of radial direction of the X-ray. However, exactly opposite to the volar teardrop there is no reproducible structure on the dorsal side. The dorsal-ulnar corner is a definable point that lies almost opposite to the volar teardrop, resulting in increased precision in DA measurement compared with Lister’s tubercle, which is located more radially.

A limitation of the study is that potential difficulties in recognising the dorsal-ulnar corner on a conventional radiograph in an accurate and precise manner were not examined. Because it is defined as the most distal edge on the dorsal side, Lister’s tubercle is easy to identify on the lateral projection. On the other hand, the dorsal-ulnar corner is defined as the second most distal edge on the dorsal side. There might be a risk for the dorsal-ulnar corner being mistaken for another nearby contour. Therefore, users of this alternative technique to measure DA need some practise to achieve high precision. In the present study the CT images could be rotated back and forth from the standardised positions, making it easy to locate the dorsal-ulnar corner on the dorsal side of the joint before the wrist was placed in the desired position. In a conventional radiograph this way of identifying the refer-
ence points is not possible. Consequently, it is reasonable to believe that the precision of the method might decrease in measuring DA on conventional radiographs because of difficulties in locating the dorsal-ulnar corner. In addition, if the radiographs were taken in slight pronation or supination, Lister’s tubercle and the dorsal-ulnar corner are no longer located strictly above each other, but in front of each other. In these cases the distinction of the dorsal-ulnar corner might be even less obvious.

A further limitation of the study is that all the examined fractures had healed in a near-anatomic position. When studying the precision of DA measurements in different positions of the wrist with alternative reference points on the joint surface it is more adequate to assess fractures with divergent displacements. The superiority of the alternative method has only been shown in DRFs with slight displacement. The results cannot be unequivocally extrapolated to more displaced fractures.

In conclusion, the precision in measuring DA in the distal radius using Lister’s tubercle as the dorsal reference point on the joint surface depends on the radial direction of the X-ray in relation to the wrist. In contrast, using the most dorsal-ulnar corner as the reference point, the DA, as it appears on radiographs, will be less dependent on the positioning of the X-ray in radial direction. However, it is more difficult to identify the proposed dorso-ulnar ridge. Therefore, the total effect on the precision of the described method when measuring DA in DRFs using conventional radiographs needs to be investigated in a separate study using radiographs of displaced fractures and several assessors.

Clinical studies

The GitRa trial (paper III and IV)

In the GitRa trial 109 patients were included (54 patients in the active group and 55 in the control group). Additionally, three patients fulfilled the inclusion and exclusion criteria at the 10-day follow-up but declined to participate and were therefore not randomised. According to the power analysis, 63 patients in each group were planned to be included. However, the inclusion period coincided with an increasing use of volar plates in displaced DRFs in 2002-2008. During this period, the indication for surgical treatment of displaced DRFs became increasingly liberal, resulting in a lower frequency of conservative treatment. The number of patients included per year was 14 in 2002, 33 in 2003, 18 in 2004, 14 in 2005, 10 in 2006, 9 in 2007 and 11 in 2008. When we noticed in 2008 that the standard deviation for the primary variable, i.e. change in DA from admission to 12 months, was smaller than anticipated and the power was high enough with the present number of patients to show the intended difference between the groups, the inclusion was
closed. The power calculations for the clinical variables were done post hoc to clarify whether the sample size was big enough for showing clinically relevant differences between the groups.

Although both the clinical and radiographic results from the active and control groups are needed to draw clinically applicable conclusions from the study, we have chosen to present the clinical and radiographic outcomes in two separate papers. There are two reasons for this decision. First, the ability of a plaster cast to prevent dislocation when stabilising a DRF needed to be elucidated. In the 1980s, considerable effort was undertaken to optimise the design of the plaster casts and plastic orthoses and find the most optimal position of the wrist joint for stable fixation. The overall conclusion from these studies was that independently of how the fractures were fixed, or in what position of the wrist joints, the radiographic results were the same between the methods studied. It gave the impression that a plaster cast had no impact on the radiographic end result of a DRF. That conclusion needed to be challenged. Why use a method that has no stabilising effect and only creates negative secondary problems? To motivate attempts for further improvement of conservative methods in the treatment of displaced DRFs a potential positive radiographic effect of a plaster cast compared with no fixation needed to be clarified.

The second reason for separating the radiographic and clinical results is that because the connection between the final deformity of the fracture and the clinical end result is weak, improved clinical end result after early mobilisation can be justified, even though the radiographic result is inferior compared with conventional plaster cast fixation time.

The two groups (active and control) were comparable in age, injured side, fracture type and initial displacement (Table 5). Although not significant, there was a tendency for the fractures in the control group to be slightly more displaced at admission in DA, RA and AC than the fractures in the active group. A thorough assessment of the randomisation procedure was therefore performed without finding any reason to believe that there was a defect in the process. We suggest that the small difference observed between the treatment groups at admission was a random effect, as the randomisation process was carried out rigorously and systematically. It is important to note that it was the fractures in the control group that were initially somewhat more displaced. Because the aim of the study was to show whether early mobilisation results in an inferior radiographic result compared with conventional fixation time, it was still possible to draw meaningful conclusions from the results.

Three patients (3/54, 6%) in the active group were excluded from the study because of failed treatment; in contrast, there were no cases of failure leading to treatment changes in the control group. The radiographs at 1 month revealed that the fractures had severely displaced in two of the
patients in the active group after removal of the plaster cast at 10 days. In one of these patient the fracture had displaced in DA, and because of constant pain and low function of the wrist, the patient underwent osteotomy, reduction and volar plate fixation after the 1-month follow-up. In the other patient RA was the most pronounced displacement. The patient reported increasing pain and disability and therefore osteotomy, reduction and dorsal plate fixation were performed 10 months after the fracture. The third patient,
classified as a failure in the active group, felt instability in the fracture immediately after removal of the plaster cast at 10 days. The patient was treated with a new plaster cast in-situ for another 3 weeks. This fracture was located slightly more proximal than the other fractures in the study, close to the transition between the metaphysis and the diaphysis. The anatomical location might have contributed to the feeling of instability. The fracture eventually healed in a good position. No other patients in the early mobilised group complained of instability after removal of the plaster cast. All radiographic and clinical parameters of the three failures were excluded from the results. The radiographic parameters of the exclusions are presented separately (Table 6).

Table 6. Radiographic results of the three excluded patients from the active group at the three follow-ups until exclusion compared with means for the active and control group. Exclusion no 1 and 2 underwent corrective osteotomies because of pain and severe displacement (shaded values). DA = dorsal angulation (degrees), RA = radial angulation (degrees), AC = axial compression (mm).

<table>
<thead>
<tr>
<th></th>
<th>Exclusion no 1</th>
<th>Exclusion no 2</th>
<th>Exclusion no 3</th>
<th>Active group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA Uninjured side</td>
<td>-8.5</td>
<td>-6.8</td>
<td>-</td>
<td>-7.0</td>
<td>-6.7</td>
</tr>
<tr>
<td>At admission</td>
<td>18.9</td>
<td>33.7</td>
<td>23.3</td>
<td>22.6</td>
<td>25.4</td>
</tr>
<tr>
<td>After reduction</td>
<td>5.2</td>
<td>16.0</td>
<td>5.2</td>
<td>4.1</td>
<td>7.7</td>
</tr>
<tr>
<td>1 week</td>
<td>1.9</td>
<td>17.1</td>
<td>0.8</td>
<td>9.0</td>
<td>14.0</td>
</tr>
<tr>
<td>1 month</td>
<td>14.5</td>
<td>42.7</td>
<td>-</td>
<td>15.0</td>
<td>15.5</td>
</tr>
<tr>
<td>12 months</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14.2</td>
<td>15.9</td>
</tr>
<tr>
<td>RA Uninjured side</td>
<td>17.3</td>
<td>19.1</td>
<td>-</td>
<td>21.7</td>
<td>21.0</td>
</tr>
<tr>
<td>At admission</td>
<td>4.3</td>
<td>10.6</td>
<td>12.0</td>
<td>15.4</td>
<td>13.7</td>
</tr>
<tr>
<td>After reduction</td>
<td>14.2</td>
<td>19.0</td>
<td>17.1</td>
<td>19.5</td>
<td>18.8</td>
</tr>
<tr>
<td>1 week</td>
<td>6.7</td>
<td>19.6</td>
<td>12</td>
<td>16.9</td>
<td>16.2</td>
</tr>
<tr>
<td>1 month</td>
<td>-0.5</td>
<td>12.8</td>
<td>-</td>
<td>13.4</td>
<td>14.7</td>
</tr>
<tr>
<td>12 months</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13.4</td>
<td>14.9</td>
</tr>
<tr>
<td>AC Uninjured side</td>
<td>-1.4</td>
<td>0.4</td>
<td>-</td>
<td>-1.2</td>
<td>-1.3</td>
</tr>
<tr>
<td>At admission</td>
<td>1.8</td>
<td>3.6</td>
<td>1.9</td>
<td>-0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>After reduction</td>
<td>-3.1</td>
<td>1.7</td>
<td>-1.4</td>
<td>-1.4</td>
<td>-1.1</td>
</tr>
<tr>
<td>1 week</td>
<td>-0.2</td>
<td>3</td>
<td>0.2</td>
<td>-0.6</td>
<td>-0.3</td>
</tr>
<tr>
<td>1 month</td>
<td>3.0</td>
<td>5.5</td>
<td>-</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>12 months</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.3</td>
<td>1.1</td>
</tr>
</tbody>
</table>

From 10 days to 1 month, i.e. the only period when the type of treatment differed between the active and control group, the early mobilised group (i.e. the active group) redisplaced significantly more than the control group in DA, RA and AC. During this period, the early mobilised group redisplaced 4.5° (p<0.001) more in DA (Figure 32 a), 2.0° (p<0.001) more in RA (Figure 32 b) and 0.5 mm (p=0.01) more in AC (Figure 32 c) compared
with the control group. Seen over the entire study, i.e. from admission to 12 months, the early mobilised group in total displaced 1.1° (p=0.48) more in DA, 3.2° (p=0.002) more in RA and 0.7 mm (p=0.02) more in AC than the control group.

There were no significant differences in grip or pinch strength at any of the follow-ups (Figure 33). At the final follow-up (12 months), both the active and control group had recovered in strength to a level that was approximately 4 kg below the grip strength of the uninjured side and approximately 0.2 kg below the pincer strength of the uninjured hand after compensation for the dominant/non-dominant hand. The figures for grip and pinch strength were also compared without compensation for the dominant/non-dominant hand, which gave the same results as when the 10% rule was applied.

At 1 month, the range of motion in dorsal extension, pronation and supination, but not in volar flexion, was significantly better in the active group:

Figure 32. a) Dorsal angulation from admission to 12 months, b) Radial angulation from admission to 12 months, c) Axial compression from admission to 12 months (mean with 95% confidence interval). Three failures in the 10-day cast group have been excluded from the analysis.
dorsal extension was $14^\circ$ ($p<0.001$), pronation $12^\circ$ ($p=0.002$) and supination $8^\circ$ ($p=0.03$) (Figure 34). With an adjustment for multiple significance test, the difference in supination was no longer significant. The significant differences found at 1 month between the groups were no longer present at subsequent data collection points (i.e. at 4 and 12 months).

The active group reported more pain than the control group at 1-month though the difference did not reach statistical significance ($p=0.06$) (Figure 35). Further, if the small difference in pain reported by the patients at 10 days were also taken into account as an expression of different baseline pain in the two groups, the difference in pain between the groups at 1 month was negligible. At 4 and 12 months, no differences in pain were observed between the two groups.

At the final 12-month follow-up, the de Bruijn scoring system (modified by Christersson & Sanden) (Figure 22), the Mayo wrist scoring chart (modified by Smith and Cooney) (Figure 23) and the Gartland and Werley De-merit wrist point system (modified by Sarmiento and by Christersson &
Figure 34. Range of motion in dorsal extension, volar flexion, pronation and supination compared with the uninjured side (mean ± 95% confidence interval). Three treatment failures in the 10-day cast group have been excluded from the analysis.

Sandén) (Figure 24) showed no differences between the active and control group (Table 7).

Three patients in the active group, but no patients in the control group, were excluded from the study. The radiographic and clinical parameters of
Table 7. Final evaluation at 12 months with three functional scoring systems (mean (SD)).

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>10-day cast</th>
<th>1-month cast</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>De Bruijn – modified</strong> (0-154; 0-15=excellent)</td>
<td>22.7 (14.3)</td>
<td>22.9 (14.9)</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Mayo – modified</strong> (0-100; 90-100=excellent)</td>
<td>74.4 (11.3)</td>
<td>73.6 (12.8)</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Gartland Werley Demerit – modified</strong> (0-35; 0-2=excellent)</td>
<td>4.8 (3.4)</td>
<td>4.3 (3.0)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

these three patients in the active group were removed from the study, except for the data concerning baseline characteristics. Because all three exclusions came from the active group, an inclusion of their results until they were excluded might have induced inflation and false improvement in the clinical results at 12 months in the active group. Therefore, we decided to exclude these patients from all follow-ups. Instead, the radiographic measurements of the three excluded fractures have been presented separately (Table 6).
Exclusion no 1 was severely displaced in RA at admission. After reduction, the displacement partially recurred until the 10-day follow-up. After the early plaster cast removal, the deformity continued to increase in RA until the follow-up at 1 month to a position even worse than at admission. The displacement in RA in this fracture at 1 month was larger than in any other fracture in the study. That the amount of RA was not included in the inclusion criteria from the beginning is a limitation of the study. In that case this fracture had perhaps not been included in the study because severe RA can be considered a contraindication to conservative treatment. However, the degree of RA has been randomly distributed between the active and control group: the more displaced fractures included in the study, the more conclusions can be drawn about the stabilising effect of a plaster cast.

Exclusion no 2 had a large displacement in DA at admission. This deformity was only partially reduced. After plaster cast removal at 10 days, the fracture continued to displace in DA until the 1-month follow-up. The displacement in DA in this fracture at 1 month was bigger than in any other fracture in the study. A limitation of the study was that there were no criteria for fracture position after reduction. It is well-known that a DRF has a higher tendency to return to its previous position after reduction if the reduction were suboptimal. According to the instructions in the GitRa trial, it was sufficient that the doctor who performed the reduction made the judgement that the post-reduction position was appropriate to continue the conservative treatment. A criterion for inclusion was also that DA at 10 days did not exceed 25°. In this way the inclusion criteria correspond more to the clinical reality in the management of DRFs and increases the possibility to generalise the results to other populations.

Exclusion no 3 was excluded because of a feeling of instability in the fracture. The patient felt movements in the fracture immediately after plaster cast removal at 10 days and insisted on being fitted with a new plaster cast. The fracture was only averagely displaced at admission, but was located a bit more proximal than most of the other fractures in the study, which could have contributed to the patient experiencing fracture movement. However, no other patients in the active or control group complained about movement between the fracture fragments.

Each of the three excluded patients had their own history preceding the exclusion event, but taken together, they suggest that removing the plaster cast before fracture healing in reduced DRFs can be adventurous, leading to an unsatisfactory outcome.

An important prerequisite for allowing early mobilisation of a reduced DRF is that the fracture position is not substantially deteriorated compared with conventional fixation time. Even though a small amount of malunion in a DRF is known to be acceptable without affecting the functional result,
there is increasing scientific support that persistent deformity can affect the clinical result, at least in young adults [48, 49, 53, 54, 169]. Therefore, an important aim in the GitRa trial was to study what happens radiographically once the plaster cast is removed 10 days after reduction in moderately displaced DRFs. It has been shown only sparingly that a conventional plaster cast fixation time of 1 month serves any useful purpose in preventing dislocation in reduced DRFs compared with shorter plaster cast fixation time [80] or semi-rigid fixation in orthosis [83]. In both these studies the active groups displaced significantly more in RA. Many studies on undisplaced or slightly displaced fractures have shown equal radiographic results between early and late plaster cast removal [75-78, 170]. It has often been stated that both reduced and not reduced DRFs can be treated with a semi-stable orthosis, allowing the wrist joint to move in some amount inside the orthosis without endangering the radiographic position [81, 82, 84, 171]. Based on these studies, our hypothesis was that a plaster cast does not contribute beyond 10 days to the preservation of a fracture position that has been achieved during reduction in a DRF. However, this hypothesis was rejected because there was a significant increase in all three directions of displacement from 10 days to 1 month, i.e. the only period when the treatment differed between the groups: DA (4.5°), RA (2.0°) and AC (0.5 mm) (Figure 32 a-c). This means that a plaster cast has a stabilising effect on a reduced DRF and prevents fracture dislocations before the fracture has healed. Whether this protective effect depends on direct support to the fracture fragments or an indirect effect by preventing joint movements cannot be established. When looking at the disparity in fracture movements between the two groups from admission to 12 months, the difference in RA (3.2°) and AC (0.7 mm) from 10 days to 1 month continued to increase until 12 months, but the difference in DA (1.1°) from 10 days to 1 month decreased to a non-significant difference until 12 months. Although statistically significant, the differences in RA and AC between the fractures in the active and control groups are relatively small. The treatment should aim to reduce the residual deformity as much as possible, but the clinical significance of such small differences in redispacements during treatment as shown in the GitRa-trial is controversial. Because conservative treatment with closed reduction and plaster cast fixation in DRFs is known to result in some improvement in DA (but not in RA and AC) compared with the displacement at admission [30, 34, 36, 172], these results are surprising. A possible reason for the absence of a positive effect on DA of plaster cast for 1 month versus 10 days from admission to 12 months in the GitRa trial is that the fractures in the control group were slightly more displaced than those in the active group at admission, especially in DA. A more dorsally angulated DRF exhibits greater instability and is more likely to redisplace after reduction. Another reason
could have been that the control group continued to displace after plaster cast removal at 1 month and therefore caught up with the DA in the active group, indicating that a fixation time of 1 month is too short. However, that was not the case.

The fractures in both treatment groups continued to displace in AC after 1 month. Although it is not certain that the final fracture position would benefit from a longer fixation time, a fixation time beyond 1 month could possibly result in an improved fracture position in AC.

In accordance with previous studies, the GitRa trial has shown that closed reduction and plaster cast fixation of DRFs in patients > 50 years lead to a partial recurrence of the initial acute displacement. The fractures in both groups healed in a position that was slightly better in DA, approximately the same in RA and slightly worse in AC compared with the displacement at admission. The radiographic study result, i.e. decreased fracture displacement in the control group compared with the active group, does not mean that plaster cast fixation of reduced DRFs is a good treatment method. Plaster cast fixation of reduced DRFs is still a poor treatment method for preservation of the fracture position. However, because 1 month of plaster cast fixation results in better radiographic outcome compared with 10 days of fixation, it could be worthwhile to improve the technique of plaster cast fixation to achieve better fracture stability. It may also be worthy to examine whether a longer fixation time results in less fracture redisplacement without deterioration of the functional outcome.

In patients under the age of 50 bone quality is often higher than in older patients, which leads to higher fracture stability and less fracture movements during conservative treatment [29, 36-39, 169]. Young patients also benefit most from rapid mobilisation in that such mobilisation can afford shorter periods of sick leave [98]. On the other hand, young adults suffer more from increased displacement compared with old people. It is important to bear in mind that the results from the GitRa trial cannot be extrapolated to patients aged < 50. Therefore, the benefits and risks of early mobilisation after reduced DRFs in young adults need to be investigated in a separate study.

In conclusion, early mobilisation at 10 days of reduced DRFs in patients >50 years led to a few more treatment failures and to slightly increased radiographic displacements in RA and AC compared with 1 month of cast fixation.

Several animal and human studies on joint immobilisation with or without concurrent injury have shown a gradual decrease in range of motion and muscle strength during the fixation period [173-177]. Ever since Sarmiento’s studies on functional bracing as a therapeutic modality in the 1970s, early mobilisation of DRFs has been regarded as preferable over immobilisation in a plaster cast until healing [81, 82]. However, scientific
support for this standpoint has been slow in evolving, both with respect to benefits in strength and range of motion. Several studies on reduced DRFs have reported early improved grip strength after early mobilisation versus conventional plaster cast fixation time but no long-term improvement [85, 87, 88, 171]. Only one study has shown persistent increased grip strength after 1 year [170]. This study, conducted on reduced DRFs in women aged > 60 years, compared immobilisation in a plaster cast for 3 weeks versus 5 weeks. In addition, concerning the range of wrist motion, several studies have shown that early mobilisation or functional bracing leads to a transient increased range compared with conventional plaster cast fixation time but no advantages in the long run [80, 86, 171, 178].

In the GitRa trial some evidence for early benefits in clinical parameters was seen. Particularly the range of motion in dorsal extension and pronation at 1 month was significantly better in the early mobilised group. Although not significant, there was a difference in grip strength (1.9 kg) and pinch strength (0.4 kg) at 1 month in favour of the active group (Figure 32). Because the difference (although not statically significant) between the two groups was consistent for both grip and pinch strength at 1 month, it may reflect a small difference between the groups. On the other hand, if the difference found in this study in grip and pinch strengths between the active and control group reflects a true difference, there is most likely no clinical relevance of such a small difference. In general, from a clinical perspective, it seems to be beneficial to remove the plaster cast at 10 days instead of 1 month. However, the difference between the two groups was small and transient. At 4 months, there were no longer any differences. The study is limited by failing to include follow-ups between 1 and 4 months. Therefore, it is not possible to state how long time after the 1-month follow-up the active group had better clinical parameters than the control group. After the 1-month follow-up, no differences between the groups in strength or range of motion were detected. A temporary gain in range of motion at 1 month can be useful for active patients, but without a relevant enhancement in grip or pinch strength we cannot be certain that it results in an improved functional capacity compared with immobilisation for 1 month.

At the 12-month follow-up (i.e. the last follow-up) the functional outcome of the two groups was evaluated using three functional assessment scores. A limitation of the study was that PROMs were not used. When the study was planned and initiated, PROMs were not available. However, objective measurements, especially grip strength, correlate with PROMs [53, 179], and all three functional assessment scores used in the GitRa trial also include questions about the patient’s subjective experience of disabilities and discomfort. Questions about the subjective result represents 88/162 points in the modified de Bruijn wrist score, 50/100 points in the modified
Mayo wrist scoring chart and 6/35 points in the modified Gartland and Werley Demerit wrist point system. We therefore believe that if there had been a difference in the subjective result between the groups, it would have been discovered.

For evaluation of pain, the patient was told to report the average pain during the past 24 hours. The prescription or actual usage of pain-relieving drugs was not recorded. We anticipated difficulties in interpreting point measurements of pain in relation to consumption of analgesics. Instead, we assessed the pain during a certain period (past 24 hours) with the assumption that the value of such a parameter is less affected by the usage of pain-relieving drugs. At the 1-month follow-up, the active group reported slightly (but not significantly) more pain than the control group \((p = 0.06)\). This difference is noteworthy in the sense that some studies have shown the opposite, i.e. early mobilisation leads to less pain compared with conventional plaster cast fixation time in undisplaced [75] and displaced [85, 170] DRFs. However, the difference in pain between the two groups at 1 month in the GitRa trial can be explained to some extent by a corresponding difference in pain at admission. Although the difference in pain at admission can hardly be regarded as a true baseline difference between the groups (pain is a parameter that changes rapidly in an unpredictable manner), the difference in pain at baseline cannot be ignored. Therefore, the interpretation of the pain assessment in the GitRa trial is that both treatments lead to the same amount of pain, or at least not to lesser pain in the active group.

In conclusion, early mobilisation of reduced DRFs led to a few treatment failures, to slightly increased radiographic displacement and had no long-standing positive clinical advantages compared with conventional immobilisation time. Early mobilisation of these fractures cannot be recommended.

The GEM trial (paper V)

There were no significant differences at enrollment between the active and control groups in age, sex, weight, length, smoking habits, working status, fractured side, hand dominance or BMD. Nor were there any differences between the active and control groups regarding the proportion of different fracture types (Table 8). The pre- and postoperative radiographs revealed no significant differences in fracture position between the two groups (Figure 37).

All 40 patients completed the follow-up according to the protocol. No serious adverse events occurred during the study period. There were three complex regional pain syndromes in the Augment® group versus one in the control group. All patients recovered after physiotherapy. No infections or signs of inflammation were observed at the fracture site in any of the patients.
Augment® patients. There were two pin infections in one patient in the Augment® group; in the control group pin infections occurred in about 18/80 (22.5%) pins in 10 patients (p=0.02 for number of infected patients and p=0.0006 for number of infected pins). No fixation pin had to be prematurely removed and all pin-related infections healed uneventfully after oral antibiotics or planned pin removal at 6 weeks (Table 9).

Table 8. Baseline characteristics of 40 patients with DRF randomised to treatment with closed reduction and external fixation alone or with the addition of rhPDGF Augment®) locally applied at the fracture site (mean and standard deviation)

<table>
<thead>
<tr>
<th></th>
<th>Augment® (n=20)</th>
<th>Controls (n=20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>1/19</td>
<td>1/19</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 ± 9.3</td>
<td>65 ± 8.2</td>
<td>0.97</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>166 ± 5.1</td>
<td>166 ± 7.4</td>
<td>0.90</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65 ± 10.2</td>
<td>71 ± 13.6</td>
<td>0.13</td>
</tr>
<tr>
<td>Injured side (dx/sin)</td>
<td>8/12</td>
<td>6/14</td>
<td>0.59</td>
</tr>
<tr>
<td>Injured side (dominant/non-dominant)</td>
<td>8/12</td>
<td>6/14</td>
<td>0.59</td>
</tr>
<tr>
<td>BMD (T-score intact wrist)</td>
<td>-1.66 ± 1.11</td>
<td>-1.14 ± 1.18</td>
<td>0.17</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>2/18</td>
<td>2/18</td>
<td>-</td>
</tr>
<tr>
<td>Fracture classification (AO):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23A3.2</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>23A3.3</td>
<td>0</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>23C2.1</td>
<td>7</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>23C2.2</td>
<td>8</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>23C3.2</td>
<td>2</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Time in external fixator, days (range)</td>
<td>42 (38-45)</td>
<td>42 (37-44)</td>
<td>0.89</td>
</tr>
</tbody>
</table>
In almost all patients in the Augment® group the postoperative radiographs revealed small amounts of β-TCP particles in the soft tissue on the dorsal side. In patients treated with Augment® Injectable, but not in patients treated with Augment® Bone Graft, there was also leakage of material into the volar soft tissue as interpreted on the postoperative radiographs (Table 10). Almost all Augment®, whether contained in the fracture void or in the surrounding soft tissues, was resorbed at 24 weeks (Figure 36).

Table 9. Complications in the Augment® and control patients

<table>
<thead>
<tr>
<th></th>
<th>Augment®</th>
<th>Control</th>
<th>P-value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pin infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>1</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Number of pins</td>
<td>2</td>
<td>18</td>
<td>0.0006</td>
</tr>
<tr>
<td><strong>CRPS(^b)</strong></td>
<td>3</td>
<td>1</td>
<td>0.30</td>
</tr>
</tbody>
</table>

\(^a\)Fischer’s exact p-value
\(^b\)Complex Regional Pain Syndrome (sympathetic reflex dystrophy)
\(^c\)at Augment® insertion site

![Figure 36. Postoperative radiograph after external fixation and dorsal injection of Augment® into the fracture gap. At 6 months, all Augment® had resolved.](image-url)
<table>
<thead>
<tr>
<th></th>
<th>Augment Bone Graft®</th>
<th>Bone Graft®</th>
<th>Augment Injectable®</th>
<th>Injectable®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Soft tissue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dorsal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>postop</td>
<td>3 (2,3)</td>
<td>3 (1,4)</td>
<td>0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>2 (1,2)</td>
<td>3 (1,3)</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks</td>
<td>0 (0,0)</td>
<td>1 (0,2)</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Volar</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>postop</td>
<td>0 (0,1)</td>
<td>3 (1,4)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>1.5 (0,2)</td>
<td>2.5 (1,3)</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks</td>
<td>0 (0,0)</td>
<td>1 (0,1)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RC joint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>postop</td>
<td>0 (0,0)</td>
<td>0 (0,0)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>0 (0,0)</td>
<td>0 (0,0)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks</td>
<td>0 (0,0)</td>
<td>0 (0,0)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DRU joint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>postop</td>
<td>0 (0,0)</td>
<td>0 (0,0)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>0 (0,0)</td>
<td>0 (0,0)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks</td>
<td>0 (0,0)</td>
<td>0 (0,0)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* arbitrary units for the amount of Augment® leakage outside the fracture: 1 = small ray, 2 = large ray, 3 = small lump, 4 = large lump.

*bre* radio-carpal joint, *c* distal radio-ulnar joint

All fractures healed during the follow-up period. At 6 weeks, no fracture was radiologically healed in either group according to the criteria used in the study, i.e. three cortices with bridging bone. At 12 weeks, 9 fractures in the Augment® group and 13 fractures in the control group were radiologically healed; all fractures were radiologically healed at the final 24-week follow-up (Table 11).

In DA and RA both groups had very similar fracture positions throughout the study. In AC the initial acute displacement was larger in the control group (2.9 mm) than in the Augment® group (1.6 mm), but the difference was not significant (p=0.11). There were no significant differences between the two groups with respect to fracture position at any follow-up visit or at the final (24-week) follow-up (Figure 37).
Clinical assessment revealed that there was no significant difference in grip strength between the groups at any time point. At 24 weeks, grip strength of the injured wrist was still reduced on an average of 41% for Augment® patients and 39% for controls (about 10 kg in absolute values) when compared with the uninjured side (Figure 38).

The patients treated with Augment® had significantly less wrist flexion at 6 weeks (9.7°, \(p=0.006\)), 12 weeks (11.4°, \(p=0.007\)) and 24 weeks (7.9°, \(p=0.03\)) compared with the control group. With an adjustment for multiple significance tests, the difference at 24 weeks was no longer significant. There were no differences between the two groups for any of the other wrist movements (Figure 39).

No statistically significant differences in DASH scores or pain (VAS) were found between the Augment® and control groups at any time point. DASH scores decreased in both groups over time, and at 6 months, the median DASH score was 6.8 in the Augment® group and 6.6 in the control group (Figure 40).

Operating time was longer in the Augment® group (42 minutes versus 29 minutes) (\(p<0.001\)), i.e. application of Augment® added an average of 13 minutes to the procedure, with no significant difference between Augment® Bone Graft or Augment® Injectable.
Figure 37 Dorsal angulation, radial angulation and axial compression on radiographs (means with 95% confidence interval). (For DA, the postop value of the Augment® group differs from the published version, see errata paper V)
Figure 38. Grip strength compared with uninjured side. The values have been adjusted according to the 10%-rule, i.e. the right hand is considered 10% stronger than the left hand in right-handed persons, but as strong as the left hand in left-handed persons.

Figure 39. Range of motion compared with the uninjured side. Extension, flexion, radial and ulnar deviations were measured at 6, 12 and 24 weeks. Supination and pronation were measured at 1, 3, 6, 12 and 24 weeks (mean with 95% confidence interval).
The main findings of the GEM trial were that Augment® (rhPDGF-BB/β-TCP) could be readily applied locally at the fracture site as intended. There were no serious adverse events in any of the patients during the observation time (24 weeks) and all fractures healed without radiographic or clinical differences between the Augment® and control groups.

Augment® has previously been tested on fractures in rats and rabbits. The safety and utility of Augment® have also been studied in periodontal osseous defects and foot fusions in humans. However, no publication has described the use of a rhPDGF-BB-containing matrix in human fractures. In this regard, the GEM trial served as a phase 1 clinical trial to evaluate the safety and feasibility of Augment® in a human fracture. We chose the DRF as a fracture template for the trial. Augment® was injected into the fracture gap of 20 DRFs. In the first 10 patients Augment® Bone Graft was used. This product, containing rhPDGF-BB and β-tricalcium phosphate, proved to be somewhat difficult to introduce percutaneously into the fracture gap. It was not possible to inject it through a cannula. Instead, we pushed the mixture through a small funnel. Even with the funnel, it was still difficult to get an even distribution of Augment® Bone Graft throughout the fracture void. Therefore, the formulation of Augment® was changed by the manufacturer. In the subsequent 10 patients Augment® Bone Graft was replaced by Augment® Injectable, which additionally contained soluble type I collagen. This additive made the drug possible to inject through a thick cannula (2.1 mm), which made it easier to distribute throughout the fracture void (Figure 41). However, the injectable properties of Augment® Injectable also increased

![Figure 40. Minimum and maximum pain, and DASH scores (medians with 25th and 75th percentile).](image)
the amount of leakage of the substance into the surrounding soft tissues, particularly on the volar side of the fracture, where very little of Augment® Bone Graft leaked out (Table 10). At the final follow-up (i.e. 24 weeks post-application), almost all Augment® Bone Graft and Augment® Injectable had resolved.

In addition to being a phase 1 clinical trial for Augment® in human fractures, the GEM trial had a modest intention to assess the potential use of Augment® in fracture healing. Therefore, a control group of 20 DRFs were added: all patients in the study (n=40) were randomly allocated to one of the two treatment groups (Augment® or control). No formal power analysis was conducted to determine an adequate sample size for this type of study.

The DRF as a fracture template for studying local application of a growth factor has advantages and disadvantages. One obvious advantage is that the DRF is a common fracture, so the desired number of patients could be reached within a reasonable period. Another advantage is that DRFs in the mid-2000s were often treated with EF. This advantage made it easier to assess the amount of bone healing because of the absence of internal fixation in the fracture area. Further, removal of the frame after 6 weeks made late fracture movements possible, which could serve as an indirect sign of incomplete fracture healing.

*Figure 41.* Augment® Bone Graft (top picture) was introduced into the fracture void through a funnel. Augment® Injectable (bottom picture) could be injected through a thick cannula.
A disadvantage of using the DRF as a fracture template when assessing the effects of a growth factor is that a DRF already has well-documented good healing properties and delayed union is rare. Therefore, it could be plausibly argued that the healing time in a DRF is already the shortest possible and hence the process cannot be further accelerated. It also proved to be a miscalculation to stabilise the fractures in EFs for 6 weeks. There was an expectation of some late fracture movements after frame removal. However, even in the control group almost no late fracture movements occurred. Consequently, this parameter was not useful to evaluate an eventful shorter healing time in the Augment® group. A post-hoc power analysis was done on changes in DA from postop to 24 weeks. With a significance level of 0.05 and a power of 80%, a difference between the groups of 4° in displacement from postop to 24 weeks could have been shown. Thus, there seems to be sufficient power to demonstrate a clinically relevant difference between the groups. However, there is a problem with this argument. The EFs were not removed until 6 weeks. Based on previous studies, we anticipated some late fracture movements [32, 69-72]. However, there were almost no fracture movements at all in DA from postop to 24 weeks in the control group. Naturally, this lack of displacement could not be enhanced by 4° in the active group. Retrospectively, it is obvious that a shorter fixation time (i.e. removal of the EFs after 4 or 5 weeks) in both groups would have been preferable. Thus, the control group might have displaced in some degree from postop to 24 weeks, a deterioration that could have been outperformed by the active group. However, we found it unethical to expose the patients to a shorter stabilisation time than usual in order to provoke a difference in displacement between the groups.

Furthermore, it is more difficult to assess the amount of fracture healing in metaphyseal bone than in diaphyseal bone. Periosteal and endosteal callus formation in cortical bone is well described but the assessment of bone healing in spongious bone is not well documented. In addition, the presence of calcium phosphate particles in the product implanted at the fracture site might be difficult to distinguish from bone. Because only a limited number of radiographic examinations are allowed within a clinical study, a subtle change in bone formation over time can also be difficult to observe. Therefore, it is not possible to detect a small difference in bone formation between the two groups.

Before injecting Augment® into the fracture gap, a small void was created at the fracture site by impacting the spongious bone inside the fracture with an elevator. This impaction created less bone volume inside the cavity and more dense bone in the margins of the void, which, together with calcium phosphate particles, made it more difficult to assess the healing of the fractures in the Augment® group. The impaction of bone could also have decreased the stability of the fractures and delayed the bone healing process.
in the Augment® group. Furthermore, Augment® does not harden. Therefore, it contributes very little to fracture stability.

BMP, previously available as Osigraft® (rhBMP-7) and InductOs® (rhBMP-2), is known to induce local signs of inflammation (swelling, effusion and redness) after application into a fracture [180]. We therefore expected similar effects of Augment®. However, no signs of inflammation around the application site were found. Accordingly, we find it unlikely that the decrease in wrist flexion detected at 6 and 12 weeks in the active group is explained by a local effect of Augment®. A more likely explanation to the decrease in wrist flexion in the active group was the pain and adhesion created by the incision and introduction of Augment® on the dorsal side of the fracture.

The finding of significantly fewer pin site infections in the Augment® group (2/80) versus the control group (18/80) was surprising and no reasonable explanation has as yet been identified. All factors known to reduce the risk for pin site infections were kept constant in all patients, making it unlikely that this finding was due to systematic error in the care or evaluation of the pin sites. In previous studies local application of a PDGF-BB-containing dressing to diabetic ulcers in the lower extremity has been shown to significantly increase the incidence of complete wound closure and shorten healing time [181], which is an expected outcome based on the biologic mode of rhPDGF-BB action. It has also been shown that hydroxyapatite, which is closely related to β-TCP, decreases the rate of pin infection when it coats the threads of the half pins [182]. Because in the present study Augment® was administered at the fracture site and not at the pin sites, there is no obvious explanation to suggest a local soft tissue effect by Augment®. The distance between the fracture site in which Augment® was introduced and where the half pins were placed, both proximally in the radius and distally in the metacarpal bone II, was approximately 5-7 cm. Although some Augment® leaked out in the dorsal soft tissue during application, this distance is probably too large for a local preventive effect against pin infection. Rather, the decrease in pin site infections might be due to a factor not directly related to the effect of PDGF-BB. For instance, a reduction in finger and movement and wrist flexion caused by pain and adhesions from the dorsal incision at the administration site in the Augment® group could have had a protective effect against pin infection. This argument is based on the notion that less soft tissue motion around the pins reduces irritation in the surrounding soft tissue. In general, the mechanism of a potential protective action against pin infection by Augment® is unclear, although not inconsistent with the established wound-healing capacity of rhPDGF-BB.

In conclusion, rhPDGF-BB/β-TCP (Augment®) is convenient to apply locally into DRFs. Within the study observation time, i.e. 24 weeks, the number of complications was not increased. No differences in clinical or
radiographic outcomes between the groups were seen, except for a small, temporary decrease in volar flexion in the active group, most likely because of the dorsal skin incision. The number of pin infections was significantly decreased in the active group, a finding that we have difficulty explaining. In this study the healing time was not reduced in the Augment® group. However, the study was neither designed nor powered to show efficacy.
Conclusions

- A semi-automatic CT-based 3D method to measure changes in DA in DRFs has the same validity as 2D radiography, but substantially higher reliability. It can therefore be used as a reference standard in cases in which precise measurements are requested. The agreement between 2D radiography and the CT-based 3D method is lower than expected based on the reliabilities of XR and CT. This lower agreement is most likely caused by the patient and method interaction effect, suggesting that the precision for DA on XR between repeated images is low.

- The precision and accuracy for measuring DA in DRFs increases when using the dorsal-ulnar corner as a reference point instead of Lister’s tubercle on the dorsal side of the joint surface.

- Mobilisation 10 days versus 1 month after reduction of moderately displaced DRFs resulted in treatment failure in 3/54 of the fractures in the active group versus no failures in the control group. Compared with the control group, fractures in the active group displaced significantly more from admission to 12 months in RA and AC, but not in DA. The clinical benefit from mobilisation 10 days after reduction, in comparison with 1 month, was a small and temporary increase in wrist motion at 1 month. Therefore, we cannot argue in favour of early mobilisation 10 days after reduction in displaced DRFs.

- rhPDGF-BB/β-TCP (Augment®) is safe and convenient for local administration into wrist fractures. In this pilot study we could not detect any reduced bone healing time in the Augment® group. However, because of the study design, efficacy could not be properly evaluated. Local administration of rhPDGF-BB/β-TCP into wrist fractures significantly decreased the number of pin infections. The mechanism of a potential protective action against pin infection by Augment® is unclear and needs to be addressed in a study with pin site infection being the primary outcome.

Denna avhandling baseras på två radiologiska och två kliniska studier. I en radiologisk studie visades att datortomografi kan användas, istället för vanlig röntgenundersökning, för att öka precisionen av en av de vinkelfelställningarna som mäts vid DRF (den s.k. dorsalbockningen). I en annan radiologisk studie visades att precisionen av mätning av samma vinkelfelställning på vanliga röntgenbilder ökar om en alternativ referenspunkt på strålbenets ledyta används, istället för den referenspunkt som vanligen ingår i mätningen.


I en annan klinisk studie på 40 DRF, som behandlades operativt med extern fixation, studerades användbarheten och säkerheten av lokal applikation i frakturspalten av Augment®, som innehåller tillväxtfaktorn rhPDGF-BB. Preparatet visade sig vara användarvänligt och säkert (under observationsti-
den 24 veckor), men p.g.a. studiedesignen var det inte möjligt att utvärdera dess effekt på benläkningen.
Future perspectives

The overall age of the population is growing (i.e. people are living longer). As people age, their risk of developing fractures, particularly DRFs, increases. Therefore, it is desirable to push the boundaries of knowledge for what subgroups of fractures and patients that can be treated conservatively and still reach a good outcome. To achieve this, the techniques in radiographic evaluation and conservative treatment need to be improved.

Fields of interest:

- To improve the validity and reliability when measuring fracture displacement on radiography, including DA, RA and AC. With informative knowledge about the correlation between malunion and persistent disability, useful treatment protocols can be developed and different treatment options can adequately be evaluated. 3D-CT can be used as a reference standard to improve the assessment of DA on radiographs while new techniques can be developed to apply 3D-CT in precise measurements of RA and AC.

- To improve conservative treatment methods to counteract fracture displacement during the fixation period: reduction techniques, design of mechanical support and fixation time.

- To select displaced fractures in young patients with good bone quality suitable for conservative treatment without endangering the radiographic position and thereby avoiding unnecessary surgical treatment.

- To evaluate the effects of rhPDGF-BB on fracture healing. In the GEM trial only radiography was used to assess bone healing. However, CT was also performed at all follow-ups. These images will be analysed and can contribute to increased knowledge about assessment of bone healing on CT, and to further elucidate the potential effects on fracture healing by rhPDGF-BB.

- To study the protective effect against pin infection of rhPDGF.
Acknowledgements

I wish to express my gratitude and appreciation to each and everyone who has made this work possible. In particular I would like to thank:

Sune Larsson, my main supervisor, for sharing me your great knowledge and experience in research, and for your guidance, time and good spirit. You supported me sincerely in all forms of adversity.

Bengt Sandén, my co-supervisor, for your brilliant mind, patience and sense of humor.

Olle Nilsson, my previous professor, for giving me the opportunity to teach and research, and for being a paragon as a physician and a human being.

Per Berg, senior consultant at the fracture unit, for sharing me your great knowledge and experience in fracture care.

Johan Nysjö, co-author in paper I and main author in Appendix 1 and 2, for productive collaboration.

Lars Beglund, co-author in paper I and statistical advisor, for making statistics a little bit more understandable.

Karin Huss, Elisabeth Belin and Sirpa Sunde, physiotherapists, for carrying out all the clinical assessments.

Gunilla Persson, nurse and coordinator at the out-patient clinic, for excellent assistance in finding appropriate patients for the clinical studies.

Håkan Bjerneld, Leif Hernefalk, Gösta Larsson, Olle Sammeli, Stefan Sundelin and Björn Thorén, consultant orthopaedic surgeons from Mora, for introducing me to Orthopaedic surgery.

Colleagues in Uppsala, especially in the fracture unit, for friendship and good atmosphere.
Kerstin and Lars Christersson, my parents, for unconditional love and support.

Malin, Johanna and Oskar, my grown-up children, for bringing me so much happiness.

Christina, my wonderful wife and best friend. You are everything to me.
Appendices
Towards User-Guided Quantitative Evaluation of Wrist Fractures in CT Images

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Abstract. The wrist is the most common location for long-bone fractures in humans. To evaluate the healing process of such fractures, it is of interest to measure the fracture displacement, particularly the angle between the joint line and the long axis of the fractured long bone. We propose to measure this angle in 3D computed tomography (CT) images of fractured wrists. As a first step towards this goal, we here present a fast and precise semi-automatic method for determining the long axis of the radius bone in CT images. To facilitate user interaction in 3D, we utilize stereo graphics, head tracking, 3D input, and haptic feedback.

1 Introduction

The standard method for examining the human skeleton after an extremity injury is conventional plain X-ray. This method has the disadvantage of being a two-dimensional (2D) image representation of a three-dimensional (3D) structure. The problem is partially overcome by acquiring images in more than one projection, and since conventional X-ray is partially transparent, it is often possible to detect fractures in the extremities. To be able to decide the correct treatment of a fracture, for example, whether a fracture needs to be operated or not, it is important to assess the fracture displacement. When a fracture is located close to a joint, for example, in the wrist, which is the most common location for fractures in humans, the angulation of the joint surface in relation to the long axis of the long bone needs to be measured [2,7]. This is illustrated in Figure 1a. Since the joint surface in the wrist is highly irregular, and since it is difficult to take X-rays of the wrist in exactly the same projections from time to time, conventional X-ray is not an optimal method for this purpose [3]. In most clinical cases, conventional X-ray is satisfactory for making a correct decision about the treatment, but when comparing two different methods of treatment, e.g., two different operation techniques, the accuracy of the angulation of the fractures before and after the treatment needs to be higher.

To overcome the limitations associated with measuring a 3D angle in a 2D projection, we propose to perform all measurements in 3D computed tomography (CT) images of the wrist (see Figure 1b). To measure the desired angle, we must
perform two tasks: (1) identify the long axis of the radius bone; and (2) identify the plane of the joint surface.

Here, we present a method for solving the first of these tasks. The proposed method is semi-automatic; the user is required to provide a bounding box for the part of the radius bone that should be used to determine the long axis. This information is subsequently used as input to an automatic algorithm that identifies the long axis with high precision. To facilitate user interaction in 3D, we use a system that supports stereo graphics, head tracking, 3D input, and haptic feedback.

2 User Interface

To provide accurate input to the automatic method, and to assess the accuracy of the results, it is vital that the user can visualize and interact with the 3D image data in an efficient way. In this section, we describe the components of the proposed user interface.
Fig. 2. An orthopedic surgeon working at the visuo-haptic display

2.1 Visualization

During user interaction, the bone regions within the CT image are displayed as shaded isosurfaces, as shown in Figure 1b. To achieve interactive frame rates, those surfaces are rendered using GPU-accelerated raycasting [6].

To enhance the user’s ability to judge depth and distances when performing the interactive axis measurements, we run our system on a stereoscopic mirror display coupled with head tracking. See Figure 2.

2.2 Haptic Interaction

Haptic interaction with 3D objects is most commonly performed with haptic devices that have one interaction point and three or six degrees of freedom (DOF). In our work, we use a PHANToM Omni device from Sensable\(^1\). The PHANToM Omni is designed as a stylus, and the haptic feedback is given at the stylus tip, the haptic probe. The device has 6-DOF for input and 3-DOF for output: it takes a position and an orientation as input; and generates a force vector as output. The device can be used with an ordinary workstation, but in our work, we have used it in combination with a specialized haptic display from SenseGraphics\(^2\) that allows for co-localized haptics and stereo graphics. This setup is shown in Figure 2.

For the task of determining the long axis of the radius bone, the haptic device serves as a 6-DOF input device that enables the user to perform precise positioning, scaling, and rotation of objects in the 3D scene.

\(^1\) http://www.sensable.com
\(^2\) http://www.sensegraphics.com
2.3 Implementation Details

We have implemented the various components of the system in C++ and Python, using an open-source software toolkit called WISH. This toolkit is intended for rapid prototyping of haptic-enabled applications (see [5] for an example) and contains implementations of various algorithms for image analysis, volume visualization, and volume haptics. For more information about WISH, please refer to the project web page\(^3\) or to [8].

3 Identifying the Long Axis of the Radius Bone

To determine the long axis of the radius bone, the user starts by placing a scalable bounding box around the part of the bone located beneath the joint, as shown in Figure 3. The position and orientation of the box is controlled via the haptic device, so that the user can pick up the box and place it in the desired location. The placement of the box does not need to be very precise, as the automatic axis computation method we will use in the next step is robust to variations in box placement.

Once the user is satisfied with the placement of the bounding box, we select all the enclosed voxels. We then use surface normal information and an adapted version of the RANSAC-based method by Chaperon and Goulette [1] to compute an accurate estimate of the long axis. The method consists of the following steps:

1. Use the marching cubes algorithm [4] to extract the surface of the selected part of the radius bone (Figure 4a).
2. Compute interpolated per-vertex normals for the extracted surface.
3. Map the surface normals to points on a unit sphere (Figure 4b). The points corresponding to surface normals that are orthogonal or near orthogonal to the long axis of the bone will form a distinct circle on the sphere.
4. Use RANSAC to iteratively fit a plane to the circle (Figure 4c). At each iteration, RANSAC will first construct a plane by randomly selecting three points from the point cloud, and then extract and count the number of points that are located within a given distance threshold from this plane. The objective here is to find the plane that maximizes the number of inliers. The normal of that plane will correspond to the direction of the long axis.
5. As a refinement step, use principal component analysis (PCA) to fit a plane to the inliers obtained in step 4. The normal of this plane will replace the normal obtained in step 4 and be selected as a candidate axis.
6. Repeat step 4–5 \(N\) times to generate a set of candidate axes.
7. Average the \(N\) candidate axes to obtain the final axis estimate (Figure 4d).

The method depends on the following parameters: the isovalue \(t_{iso}\) used for surface extraction; the distance threshold \(t_{dist} \in [0, 1]\) used for outlier removal; the number of iterations \(K\) performed by RANSAC; and the number of repetitions \(N\). The value of \(t_{iso}\) should be based on the Hounsfield unit (HU) value for bone.

\(^3\) http://www.cb.uu.se/research/haptics/
tissue. The value of $t_{\text{dist}}$ translates into an angle and can be estimated using a priori shape information about the bone. $K$ should be set to a high value to ensure, with a reasonable high probability, that at least one plane with a good fit to the circle is selected. Experimentally, we have found $K = 1000$ to be sufficient for our datasets. Finally, the value of $N$ should also be set high, e.g., $N = 100$. Axes produced by single runs of RANSAC tend to be slightly misaligned, but by running RANSAC several times and averaging the results, we can obtain an accurate estimate of the desired axis.

A similar method was presented by Winkelbach et al. [9], who used surface normal information and a Hough-transform voting scheme to measure the axes of cylindrical bone fragments. That method, however, can only be used for cylindrical surfaces. In Figures 3 and 4, we can see that the part of the radius bone that we are interested in performing axis measurements on is conical rather than cylindrical. Hence, the method of [9] would not be able to find the desired axis in our case.
4 Experiment and Results

For this experiment, we used 14 CT images of fractured wrists. The images have the dimensions $512 \times 512 \times N_z$, where the number of slices $N_z$ ranges from 92 to 243. The pixel resolution is between 0.2 and 0.4 mm and the slice thickness ranges from 0.8 to 1.0 mm. Before loading the CT images into our system, we converted them from stacks of DICOM images to 8-bit VTK volume images with graylevel values between 0 and 255.

One user (an orthopedic surgeon) performed repeated axis measurements on the 14 CT images using the proposed system. A short training session allowed the user to become familiar with the system before the measurements started. The user repeated the measurements three times for each image, and was, to reduce learning bias, instructed to change image after each measurement. The axes were computed using the method described in Section 3, with the fixed parameters $t_{iso} = 90$ (which corresponds to 1084 HU), $t_{dist} = 0.25$ (which corresponds to a 14 degree angle), $K = 1000$, and $N = 100$. In total, 42 axes were measured.
Table 1. The geodesic distances (in degrees) between the axes $A_1$, $A_2$, and $A_3$ that one user obtained by performing repeated axis measurements on the radius bone in 14 CT wrist images.

<table>
<thead>
<tr>
<th>Wrist image</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<th>11</th>
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<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1A2</td>
<td>0.43</td>
<td>0.23</td>
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<td>0.95</td>
<td>0.56</td>
<td>0.17</td>
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<td>0.86</td>
<td>1.23</td>
<td>0.35</td>
<td>0.36</td>
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</tr>
<tr>
<td>A1A3</td>
<td>0.37</td>
<td>0.29</td>
<td>0.18</td>
<td>0.23</td>
<td>1.03</td>
<td>0.68</td>
<td>0.50</td>
<td>1.33</td>
<td>0.10</td>
<td>0.23</td>
<td>0.26</td>
<td>0.83</td>
<td>0.62</td>
<td>0.18</td>
</tr>
<tr>
<td>A2A3</td>
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<td>0.11</td>
<td>0.17</td>
<td>0.19</td>
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<td>0.18</td>
<td>0.32</td>
<td>0.87</td>
<td>0.78</td>
<td>0.59</td>
<td>1.28</td>
<td>1.15</td>
<td>0.36</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Fig. 5. The axis measurement results obtained for (a) wrist 1, (b) wrist 7, and (c) wrist 12. Note that each image shows three (mostly overlapping) axes that have been computed with different bounding boxes.

The 42 axis measurements required, on average, an interaction time of $\sim 20$ seconds and a computational time of $20 \pm 5$ seconds. To assess intra-user precision, we represented the obtained axes as points on a unit sphere and computed, for each axis triplet $\{A_1, A_2, A_3\}$, the geodesic distances between the points. Table 1 shows the resulting distance values expressed in degrees. The overall small distance values achieved indicate that our method has a high repeatability and is robust to variations in the placement of the bounding box. Figure 5 illustrates the axis measurement results. Shifting the parameter values $\pm 15\%$ caused only slight (on average, less than 0.5 degrees) differences in the measurement results, indicating that the method is fairly robust to the choice of parameter values. Since we have performed the measurements on real data, there is no ground truth available to verify the obtained axes against. The axes have, however, been visually inspected and deemed acceptable for their intended usage.

5 Conclusions

As stated in the introduction, our goal in this project is to develop a robust and accurate method for measuring the angulation of the joint surface in relation to the long axis of the radius bone in CT images of fractured wrists. Here, we
have presented a method for solving the first part of this task: to determine the long axis of the radius bone. In an empirical study, we have demonstrated that the proposed method allows the long axis to be determined with high precision, with only limited user input. The overall measurement procedure takes less than 1 minute to perform, making the method suitable for interactive use.

To facilitate user interaction in 3D, we have implemented the proposed method in a system that utilizes stereo graphics, head tracking, and haptic feedback. In addition to enabling precise quantitative measurements, we believe that this user interface is of great value for qualitative assessment of wrist fractures. Initial response from orthopedic surgeons who have tested the system has been very positive. Next, we plan to complete the system with a method for determining the orientation of the joint surface.

**References**

Precise 3D Angle Measurements in CT Wrist Images

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\textbf{Abstract.} The clinically established method to assess the displacement of a distal radius fracture is to manually measure two reference angles, the dorsal angle and the radial angle, in consecutive 2D X-ray images of the wrist. This approach has the disadvantage of being sensitive to operator errors since the measurements are performed on 2D projections of a 3D structure. In this paper, we present a semi-automatic system for measuring relative changes in the dorsal angle in 3D computed tomography (CT) images of fractured wrists. We evaluate the proposed 3D measurement method on 28 post-operative CT images of fractured wrists and compare it with the radiographic 2D measurement method used in clinical practice. The results show that our proposed 3D measurement method has a high intra- and inter-operator precision and is more precise and robust than the conventional 2D measurement method.

\textbf{Keywords:} Wrist fractures, CT, angle measurements, bone segmentation, interactive mesh segmentation, surface registration

1 Introduction

Distal radius fractures occur when the radius bone in the wrist breaks between the shaft and the joint surface. The clinically established method to assess the displacement of such fractures is to manually measure two reference angles, the dorsal angle and the radial angle, in 2D X-ray images of the wrist [4], as illustrated in Fig. 1. Although this approach usually works well enough for diagnosis and treatment-guidance in clinical practice, it has the disadvantage of being sensitive to operator errors since the angle measurements are performed on 2D projections of 3D structures. An intra- and inter-operator variability of 3–4° has been reported [4,5], which is too high for, e.g., orthopedic research studies where more precise angle measurements are required to compare different methods of treatment. The lack of depth in X-ray images makes it difficult to assess the 3D positions of the bone structures. Moreover, consecutive X-ray images are seldom acquired at exactly the same angle, and the contours of the bones are often smooth, which makes it difficult to define reliable landmarks for the measurements. In this paper, we aim to overcome these issues and precision limitations by measuring the dorsal angle in 3D computed tomography (CT) images.
Fig. 1: (a) Frontal X-ray image of a distal radius fracture. The arrow marks the fracture location. (b) The dorsal angle, \( \theta \), measured in 2D on a lateral X-ray image of the same wrist. \( \theta \) is defined as the angle between the joint line \( JL \) and a line that is orthogonal to the long axis \( RA \) of the radius. (c) A 3D rendering showing the radius bone and the reference axes we need to identify to measure the dorsal angle in 3D.

To measure the dorsal angle in 3D, we need to identify two components: (1) the long axis \( RA \) of the radius shaft; and (2) a local reference coordinate system \((X_r, Y_r, Z_r)\) defining the orientation of the joint surface. These components are illustrated in Fig. 1c. The first component, the long axis, can be identified using surface normal information and random sampling consensus (RANSAC), as proposed in [9]. In this paper, we focus on the second component, presenting a precise semi-automatic method for identifying and tracking the orientation of the joint surface over time. By combining this method with the previously presented axis estimation method [9], we obtain a system that can be used to measure relative changes in the dorsal angle in 3D CT images of fractured wrists.

2 Image Data and Preprocessing

The image data used here consists of 28 post-operative CT images of fractured wrists in six patients. Each patient was scanned at 4–6 different occasions, 0–24 weeks after surgery. The CT images were acquired with a pixel spacing of 0.16–0.39 mm and a slice thickness of 0.4–0.8 mm. The original image dimensions were \( 512 \times 512 \times N_z \) voxels, where the number of slices, \( N_z \), ranged from 72–346. We converted each of these CT images from a stack of 16-bit DICOM images with grayscale values between -1024 and 3071 to an 8-bit VTK volume image
with normalized graylevel values between 0 and 255. Thereafter, we cropped the converted CT images closely around the radius to reduce the amount of data and speed up processing. We subsequently reflected left wrists into right wrists to simplify the construction of reference coordinate systems (our method assumes a right-handed coordinate system). Finally, we resampled the volume data from anisotropic to isotropic voxel size using cubic interpolation.

3 Identifying and Tracking the Joint Surface Orientation

This section describes our proposed semi-automatic method for identifying and tracking the orientation of the joint surface of a fractured radius over time. The method consists of three main steps: segmentation, template generation, and surface registration.

3.1 Segmentation

The first task is to create an accurate surface-mesh representation of the radius. The radius shaft is mainly composed of dense (cortical) bone, which appears significantly brighter than other tissue types in CT and is straightforward to segment using, for instance, global thresholding. The joint surface, on the other hand, needs to be more flexible and is therefore composed of spongy (trabecular) bone, of which intensity distribution partly overlaps that of skin and soft-tissue. Because of this intensity overlap, simple intensity-based segmentation methods such as global thresholding cannot completely separate the radius from the rest of the image. The segmentation task is further complicated by partial volume effects (PVE) and the, in comparison with the image resolution, very narrow spacing between the articulated surfaces of the wrist bones. This leads to blurring of the joint boundaries, making it difficult to separate the wrist bones from each other even though they are not actually connected.

A common approach to deal with intensity inhomogeneities and image imprecisions is to use segmentation methods that not only consider the intensity of the voxels but also their spatial relationships. One such method is hysteresis thresholding [3], where the idea is to (1) define an upper threshold \( t_{\text{high}} \) and a lower threshold \( t_{\text{low}} \) for the object of interest, (2) threshold the image at \( t_{\text{high}} \) to generate a set of bright seed voxels that are assumed to belong completely to the object of interest, (3) threshold the image at \( t_{\text{low}} \) to extract darker candidate object voxels, and (4) apply connectivity analysis to identify and remove all candidate object voxels that are not connected to at least one seed voxel. This method lends itself well for segmenting bone in CT since the approximate Hounsfield unit (HU) ranges for cortical and trabecular bone are known.

We segmented the wrist bones using hysteresis thresholding with fixed thresholds \( t_{\text{low}} = 76 \) and \( t_{\text{high}} = 89 \), which correspond to the lower intensity range for trabecular and cortical bone, respectively. We then used the marching cubes algorithm [8] to generate a triangular mesh representation of the segmented bones, which, to reduce staircase artifacts, had been postprocessed with a Gaussian
smoothing kernel of size $\sigma = 0.7$ mm. The resulting mesh was simplified from on average 1,000K triangles to 340K triangles using the vtkDecimatePro filter from the Visualization Toolkit (VTK) library\(^3\) and moderately smoothed with a Laplacian filter (20 iterations, relaxation factor 0.1) to improve the mesh quality. Thereafter, we used interactive mesh-cutting by random walks [7] to separate the radius from the carpal bones and the ulna. Figures 2 and 3 illustrate the segmentation process. The sketch-based seeding interface allows the user to draw seeds directly on the surface mesh and was implemented using 3D ray-picking accelerated by an octree.

### 3.2 Template Generation

Having segmented the radius, our next task is to construct a template of the joint surface. We also need to derive a local reference coordinate system for this template that can be used to describe the orientation of the joint surface.

Building a statistical shape model of the joint surface is difficult due to the high shape-variability of the radius. Instead, we use the joint surface in the first postoperative CT image as template and construct a local reference coordinate system (similar to that in [6]) from user-defined landmarks. Figure 4 illustrates the idea. The user has to perform two interactive tasks: (1) select three landmarks corresponding to the small peaks located at the corners of the joint surface; and (2) position a 3D cutting plane so that it separates the joint surface from the radius shaft and the fracture. To keep the interaction task as simple as possible, the cutting plane is initially aligned to the landmarks and cannot be scaled or rotated but only translated along its normal direction. We define

\(^3\) URL: http://www.vtk.org/
an initial reference coordinate system \((X'_r, Y'_r, Z'_r)\) as follows: \(Y'_r = l_1 - \frac{l_2 + l_3}{2}\); \(Z'_r = (l_1 - l_2) \times (l_3 - l_2)\); and \(X'_r = Z'_r \times Y'_r\). The actual reference coordinate system \((X_r, Y_r, Z_r)\) is then obtained by applying a transform \(R\) that performs a 20-degree counterclockwise rotation of \((X'_r, Y'_r, Z'_r)\) about \(X'_r\), so that \(X_r = X'_r\), \(Y_r = RY'_r\), and \(Z_r = RZ'_r\). The rotation corresponds roughly to the normal radial angle [5] in intact wrists and is required to align the axes correctly. \(X_r\) corresponds to the reference line \(JL\) shown in Fig. 1b. The landmarks positioning does not need to be very precise, but must be performed as indicated in Fig. 4.

### 3.3 Surface Registration

The third and final task is to register the template mesh extracted from the first postoperative CT image against the radius meshes extracted from the remaining \(n - 1\) follow-up images in the CT scan sequence, so that we can determine the orientation of the joint surface in each image. To accomplish this, we developed a semi-automatic surface registration interface based on the iterative closest point (ICP) [2] algorithm. The registration is performed in two steps:

1. Coarse alignment of the template by procrustes analysis of user-defined landmarks.
2. Precise surface registration using a modified ICP algorithm, with the template as source mesh and the segmented radius as target mesh.

Figure 5 illustrates the registration process. Step 1 is required because ICP needs a good starting guess to produce accurate registration results. After applying ICP, we obtain a rigid-body transformation that, together with the local reference axes of the template, defines the orientation of the target joint surface.
Fig. 4: Generation of a joint-surface template. The local reference coordinate system shown in the lower right image is derived from the three landmarks.

The original ICP algorithm described in [2] assumes that the input data is outlier-free and, further, that every point in the source mesh corresponds to a point in the target mesh. Unfortunately, neither of these assumptions holds for our data: due to segmentation errors and various CT image artifacts, the template might not overlap the target mesh completely, and even if perfect segmentation results were available, the joint surface might be fractured and have small disconnected fragments that move around during the healing. Furthermore, the original ICP algorithm does not take surface normal information into account, which means that there is no guarantee that it will actually fit the outer or the inner surface of the template to the corresponding surface of the radius. Our initial experiments with ICP showed that even with a good initialization, the algorithm can produce poor registration results by, for instance, fitting the outer surface of the template to the inner surface of the radius.

To remedy these problems, we implemented a modified ICP algorithm that, in every iteration, (1) identifies and rejects all closest point pairs of which normal directions differ more than 90 degrees and (2) rejects 10% of the remaining point pairs with the largest point-to-point distances. The second rejection criteria
makes the algorithm more robust to segmentation errors. The implementation is entirely CPU-based and uses a kd-tree for accelerated closest-point search.

3.4 Implementation Details

We implemented the proposed segmentation and registration pipeline using VTK, Python\textsuperscript{4}, and NumPy/SciPy\textsuperscript{5}. To solve the sparse linear system \cite{7} generated in the mesh-segmentation step, we used a Ruge-Stüben-based algebraic multigrid solver obtained from the PyAMG library \cite{1}.

4 Computing the Dorsal Angle

Using the reference axes $RA$ and $X_r$ extracted with the methods described in \cite{9} and in Section 3, respectively, we compute the dorsal angle $\theta$ as

$$\theta = \frac{\pi}{2} - \arccos(RA \cdot X_r).$$  

5 Experiments and Results

Two test users performed repeated 3D angle measurements on the six CT scan sequences described in Section 2. The first user (U1) was an orthopedic surgeon with long experience of measuring wrist angles in 2D, whereas the second

\textsuperscript{4} URL: http://www.python.org/
\textsuperscript{5} URL: http://www.scipy.org/SciPy/
user (U2) was a PhD student in image analysis who had no prior experience of evaluating wrist fractures. The first user had not used the system before and therefore received a short training session before the experiment started. Each user repeated the measurements five times on the four CT scan sequences that included most samples and two times on the remaining two CT scan sequences, measuring 111 angles in total. The experiments were performed on a laptop equipped with an Intel Core i7-3612QM 2.1 GHz CPU, 8 GB DDR3 RAM, an Intel HD Graphics 4000 GPU, and 64-bit Ubuntu Linux 12.04. In addition, one of the users (U1) performed conventional 2D angle measurements on plain X-ray images that had been acquired at the same occasions as the CT images.

Figures 6 and 7 illustrate the angle measurement results. The intra-operator precision (mean angle difference $\pm$ 1.96 SD) of the 3D measurement method was $0.07 \pm 0.74^\circ$ for user U1 and $0.21 \pm 0.56^\circ$ for user U2, and the inter-operator precision was $0.19 \pm 1.09^\circ$, indicating high repeatability. The intra-operator precision of the 2D measurement method was considerably lower, $-0.05 \pm 4.82^\circ$, confirming the limitations of the method. The mean computational time required to process a single CT image was $21.8 \pm 7.0$ seconds: $3.7 \pm 2.2$ s for hysteresis thresholding, $4.8 \pm 3.2$ s for surface extraction, $4.0 \pm 1.1$ s for random walks, $7.7 \pm 2.4$ s for ICP registration, and $1.6 \pm 0.6$ s for RANSAC axis estimation. The total time (interaction time plus computational time) required to process a sequence of five CT images was $\sim 10$ minutes. There is no ground truth available to verify the obtained angles against, but the segmentation and registration results were considered successful in all trials, and the obtained axes $RA$ and $XR$ have been visually inspected and deemed accurate enough.

6 Conclusion

We have presented a semi-automatic method for identifying and tracking the orientation of the radius joint surface in 3D CT images of fractured wrists. By combining this method with a previously developed method for identifying the long axis of the radius, we have also developed a system that enables precise 3D measurements of relative changes in the dorsal angle, one of the reference angles orthopedic surgeons use to assess the displacement of wrist fractures. The results presented in this paper show that our proposed 3D angle measurement method has a high intra-and inter-operator precision and is more precise than the conventional 2D measurement method used in clinical practice. The system is efficient enough for interactive usage and allows a user with no prior experience of evaluating wrist fractures to achieve similar results as an expert.

Next, we plan to deploy the presented system in orthopedic research studies where the objective is to compare different methods of fracture treatment. We also plan to extend the system so that it can be used to measure relative changes in other 3D rotation angles defined for the wrist, for instance, the radial angle [4]. Finally, we aim to further improve the robustness and accuracy of the angle measurement method. This could be achieved by, for instance, automa-
Fig. 6: Relative dorsal angles obtained in five trials with our proposed 3D measurement method (3D CT) and the conventional 2D measurement method (2D X-ray). U1 and U2 denote the two test users who performed the repeat measurements. The vertical bars show the mean and the range of the angles.

Modifying some of the interactive steps or replacing the underlying surface-based segmentation and registration methods with volumetric counterparts.

References

Fig. 7: Bland-Altman plots illustrating the intra- and inter-operator precision of the evaluated methods and the agreement between the 2D and 3D angle measurements. The solid line represents the mean angle difference, whereas the dashed lines represent ±1.96 SD of the angle difference.

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