Internal Fixation of Femoral Neck Fractures; treatment and effects

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Colofon

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Voor

Jouke (13 februari 1980 – 26 januari 2008)
en
Papa (22 mei 1948 – 15 juli 2008)

Table of contents

Chapter 1

Introduction

Hip fractures are a major global health problem. They are associated with one year mortality rates reported around 20 to 30% and a profound impairment of independence and quality of life.[1-3] Up to 50% of hip fracture patients do not rehabilitate to their pre-fracture ambulatory or functional status.[4,5] The disability adjusted life-years lost as a result of hip fractures ranks in the top 10 of all cause disability globally.[1]

The worldwide occurrence of hip fractures increased from an estimated 1.3 million patients per year in 1990 to 1.6 million in 2000.[1,6] In the Netherlands, the occurrence of hip fractures has increased from 7,614 patients per year in 1981 to 21,000 in 2010.[7,8] Despite a declining trend of (age-adjusted) incidence in western countries, a worldwide increase in total number of hip fractures is still expected as a result of increasing age-adjusted incidence rates in developing countries and aging populations by improved global health care.[8,9]

The health care costs associated with hip fracture care are considerable. Globally, the annual estimated worldwide direct and indirect costs of hip fractures amounted to $34.8 billion in 1990, and are expected to rise to an estimated $131 billion by 2050.[10] In the Netherlands, the total costs of hip fractures care amounted to € 378 million in 2007.[11] This was 0.5% of the total cost of Dutch health care, and 2.4% of the cost of Dutch hospital care in 2007.

The treatment of hip fracture patients is based upon the anatomical location of the fracture. Hip fractures can be extracapsular (*i.e.*, inter-/subtrochanteric) or intracapsular (*i.e.,* femoral head and neck). Approximately 50% of all hip fractures are intracapsular fractures of the femoral neck.[12] These fractures can be treated operatively with internal fixation or arthroplasty. This thesis is focused on the treatment of femoral neck fracture patients with internal fixation.

From meta-analyses it is known that internal fixation may lead to lower infection rates, less blood loss, a shorter operative time, and possibly a decrease in mortality rate, compared with arthroplasty. In contrast, arthroplasty significantly reduces the revision surgery rate, which is an important advantage, as revision surgery rates of approximately 35% have been reported after internal fixation failure.[13-16] The main indications for revision surgery after internal fixation are non-union, avascular necrosis of the femoral head, or implant failure.

The decision between internal fixation and arthroplasty is based upon patient characteristics and fracture displacement (Figure 1). Patients with undisplaced fractures (*i.e.,* Garden 1 or 2) should be treated with internal fixation.[12] However, femoral neck fracture patients with arthrosis, rheumatoid arthritis, or a pathologic fracture should be treated with arthroplasty, as these conditions are contraindications for internal fixation. Elderly *(i.e*., >80 years old) with a displaced fracture (*i.e;* Garden 3 or 4) should receive arthroplasty. However, there is no clear consensus on the treatment of younger patients with a displaced fracture.[14,15,17-21] The general opinion seems to be that internal fixation can be used in patients with limited comorbidity,

who are mobile, independent, and not cognitively disabled pre-fracture. Patients for whom the risk of revision surgery is considered too high should be treated with arthroplasty. These evidence-based considerations on the treatment of femoral neck fractures were summarized by the Association of Surgeons of the Netherlands (ASN/NVvH) in 2007 in an evidence-based guideline on the treatment of elderly hip fracture patients.[22]

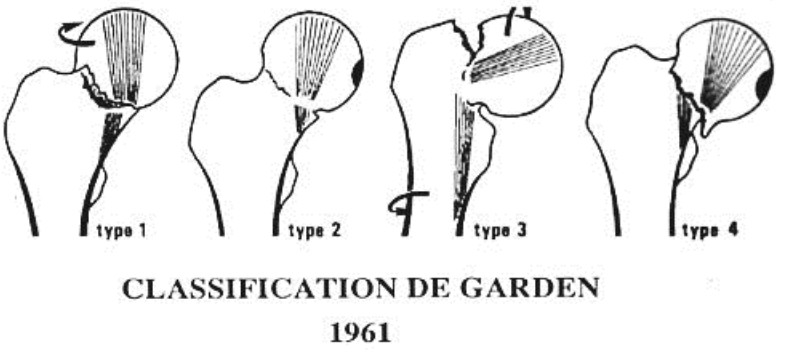

Figure 1. Garden classification

After internal fixation has been decided on, the type of implant has to be selected. The dynamic hip screw (DHS) or multiple cancellous screws (CS) are still most commonly used (Figure 2). Newer (usually angular stable) implants, such as the Targon® FN or the dynamic locking blade plate (DLBP), are being investigated but are not used frequently yet.[23-25] Consensus on the preferred implant is currently lacking and surgical preference may play a role.[13,19] The international FAITH study (Fixation using Alternative Implants for the Treatment of Hip fractures, NCT00761813) is aimed to resolve the debate on the best implant for internal fixation of femoral neck fractures, comparing angular stable (DHS) versus non-angular stable implants (CS). A summary of the aims and methods of the FAITH study is provided in Appendix 1. Data from the Dutch FAITH study were used in this thesis to study topics concerning internal fixation of femoral neck fracture patients, that have previously received insufficient attention in the literature.

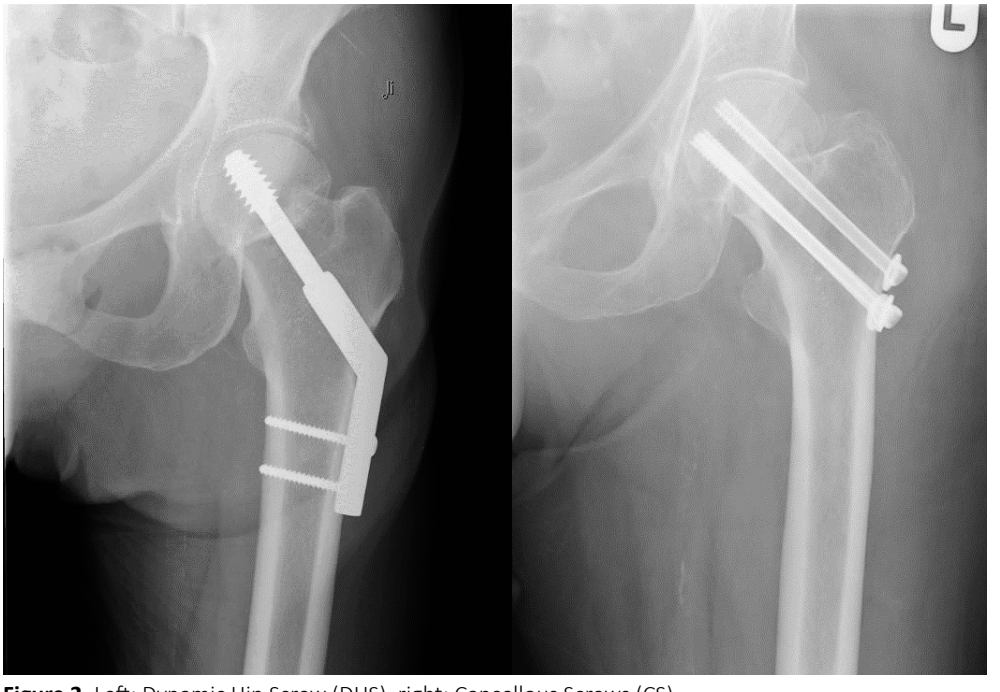

Figure 2. Left: Dynamic Hip Screw (DHS), right: Cancellous Screws (CS)

Aim of the thesis

The aim of this thesis was to analyze the extent to which the current treatment of femoral neck fracture patients with internal fixation is uniform and in agreement with the national guideline. The second aim was to study the effect of internal fixation on health care costs and functional outcome.

Randomized controlled trials (RCTs) are still relatively scarce in the orthopedic trauma literature. This may be attributed to the logistical challenges of the implementation of RCTs. **Part 1** of this thesis is therefore focused on how to perform RCTs in trauma research. In **Chapter 2** different trial management strategies to organize and conduct a multicenter RCT are compared. Trial management by a single financed national trial coordinator is compared with management by individual local site coordinators in a per patient payment system. The effect of these strategies on performance of the FAITH trial is described. In **Chapter 3** an overview of the guideline for Good Clinical Practice (GCP) in the context of conducting an implant trial in orthopedic trauma surgery is provided.

In the past, the femoral neck fracture was also named 'the unsolved fracture', as discussion persisted on the best treatment for various patient categories. Therefore, studies on femoral neck fracture treatment have focused on defining indications for the different

surgical procedures. The available evidence was summarized in a national guideline. **Part 2** of this thesis is focused on analyzing the extent to which the current treatment of femoral neck fracture patients with internal fixation is uniform and in agreement with the national guideline. The implications of treatment with internal fixation on health care costs are also described. In **Chapter 4** the extent to which femoral neck fracture patients are treated in agreement with the national guideline is determined. As indicated in the guideline and literature, for some patient groups (*i.e.,* younger, relatively healthy patients with a displaced fracture) there is still a need to define what treatment is most beneficial. As evidence is not conclusive yet, we hypothesized that treatment of these patient subgroups may still not be uniform. Because the guideline states that treatment decision should be based upon patient and fracture characteristics, differences in these characteristics between the treatment groups are also determined. In **Chapter 5** the characteristics and treatment of patients with non-simultaneous bilateral femoral neck fractures are studied, in order to analyze if similar characteristics at the time of both fractures lead to similarity in treatment. The cumulative incidence of bilateral neck fractures and mortality in these patients is also described. In **Chapter 6** a detailed overview is provided of the cost and healthcare consumption of patients treated for a femoral neck fracture with internal fixation. Detailed information on health care costs are gaining importance as the burden of health care costs threatens to exceed the available financial resources. It is therefore necessary to focus on options to cut down health care expenses. In order to study the burden of extra costs caused by revision surgeries, costs of patients who underwent revision surgery are compared with costs of patients who did not.

Research on the outcome of treatment of femoral neck fractures with internal fixation is traditionally aimed at fracture healing, revision surgery, morbidity, and mortality. However, little is known about the physical limitations that may result from internal fixation. If functional outcome is measured, it is often done using self-reported quality of life questionnaires only. In **Part 3** the functional outcome of femoral neck fracture patients treated with internal fixation is studied in more detail. In **Chapter 7** femoral neck shortening is measured in patients who sustained a femoral neck fracture treated with internal fixation at least one year before. Femoral neck shortening may occur due to the implant allowing fracture fragments to slide along the implant and permitting impaction at the fracture site, especially when subjected to an axial loading force during weight bearing. Risk factors for femoral neck shortening are determined, as well as the effect of femoral neck shortening on gait pattern and muscle strength. In a secondary cohort study in **Chapter 8** functional outcome of patients after salvage arthroplasty for failed internal fixation is compared with outcome of patients who healed uneventfully after internal fixation of a femoral neck fracture. Patient independency, health-related and disease-specific quality of life, gait pattern, and muscle strength are compared between the two groups in order to determine if outcome after salvage arthroplasty is satisfactory. In **Chapter 9** patients who had their implant removed

after internal fixation of a femoral neck fracture are studied. Knowledge on the effect of implant removal on physical functioning is limited. Therefore, the effect of implant removal on health-related quality of life and disease-specific quality of life is studied in a matched pair analysis. Patient characteristics of the implant removal patients are described in order to get more insight into which patients had their implant removed. In order to retrieve independent functioning after hip fracture surgery physical therapy is important. In **Chapter 10** the structure and intensity of the physical therapy that femoral neck fracture patients treated with internal fixation receive after hospital discharge is described in detail. There is currently no information on how this is done in daily practice. As recent studies have suggested that benefits of an intensified rehabilitation program may exist, an attempt was made to identify a subgroup of patients that could benefit more from an extended therapy program. Therefore, the characteristics of patients who had a short period of therapy (*i.e.*, <6 months) and a longer period of therapy (*i.e.*, ≥6 months) are compared.

In **Chapter 11** the main results and conclusions of the studies in this thesis are summarized, a Dutch translation is provided in **Chapter 12**. Finally, in **Chapter 13** a general discussion of the main findings in this thesis and its consequences on treatment of patients with femoral neck fractures is provided, including future perspectives.

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Part I

Chapter 2

Central coordination as an alternative for local coordination in a multicenter randomized controlled trial: the FAITH trial experience

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Abstract

Background: Surgeons in the Netherlands, Canada and the US participate in the FAITH trial (Fixation using Alternative Implants for the Treatment of Hip fractures). Dutch sites are managed and visited by a financed central trial coordinator, whereas most Canadian and US sites have local study coordinators and receive per patient payment. This study was aimed to assess how these different trial management strategies affected trial performance.

Methods: Details related to obtaining ethics approval, time to trial start-up, inclusion, and percentage completed follow-ups were collected for each trial site and compared. Pre-trial screening data were compared with actual inclusion rates.

Results: Median trial start-up ranged from 41 days (P25-P75 10–139) in the Netherlands to 232 days (P25-P75 98–423) in Canada (p=0.027). The inclusion rate was highest in the Netherlands; median 1.03 patients (P25-P75 0.43–2.21) per site per month, representing 34.4% of the total eligible population. It was lowest in Canada; 0.14 inclusions (P25-P75 0.00–0.28), representing 3.9% of eligible patients (p<0.001). The percentage completed follow-ups was 83% for Canadian and Dutch sites and 70% for US sites (p= 0.217).

Conclusions: In this trial, a central financed trial coordinator to manage all trial related tasks in participating sites resulted in better trial progression and a similar follow-up. It is therefore a suitable alternative for appointing these tasks to local research assistants. The central coordinator approach can enable smaller regional hospitals to participate in multicenter randomized controlled trials. Circumstances such as available budget, sample size, and geographical area should however be taken into account when choosing a management strategy.

Trial registry: Clinical trial registration number: FAITH trial, (NCT00761813).

Introduction

Randomized controlled trials (RCTs) are generally perceived as the reference standard for generating valid scientific evidence on the evaluation of medical treatments and interventions.[1] Unfortunately, RCTs continue to be relatively scarce in the orthopedic trauma literature.[2] This may be attributed to the logistical challenges of the implementation of RCTs.

One of the most apparent challenges of RCTs is to recruit the required number of patients as timely and efficiently as possible.[3] Availability of fewer patients than expected usually leads to an extended trial period and increased costs. Multicenter collaborations offer the potential of recruiting more patients within a shorter time period, which can be advantageous if large patient numbers are required or if the targeted population has a low incidence. They also have the advantage of increased generalizability of the results.[4,5] However, the conduct of multicenter clinical trials requires a complex organization, which applies even more to international trials.[6,7]

Obtaining ethics or Institutional Review Board (IRB) approval is a potential cause of delay, as procedures, documents, and legislation may vary between countries.[8] This process is often time-consuming and it is recommended to have dedicated and well-trained study personnel available to assist participating sites with these administrative tasks.[9-13]

Another challenge in multicenter research is the selection and recruitment of appropriate participating clinical sites. Every participating site should have a devoted and dedicated clinician as site principal investigator. As surgeons often lack the time to spend on research, it is important to have an assisting research team that can adopt many of the time consuming research tasks. Having adequate support can be more important for sites to decide to participate, than offering a financial compensation for participation.[14,15] The presence of a trial coordinator or assistant will also facilitate an appropriate study infrastructure, which is a requirement for proper study conduct.[3,8,16-18] As community hospitals generally lack such infrastructure, they often cannot participate in multicenter trials. This is unfortunate, as some injuries or interventions are much more frequent in community hospitals than in university hospitals. Their participation in a multicenter trial could therefore positively influence the recruitment rate. Once a large multicenter or multinational RCT has started, a relatively complex organization should be implemented and maintained in order to assure a complete patient follow-up and a high quality in data management.[19,20]

Usually individual sites are required to manage their local ethics procedures and trial logistics. They generally receive per patient payments as compensation. As an alternative option, a single trial coordinator can be appointed to manage all trial-related tasks for multiple sites in a certain geographic area or country, in which travel time is limited and does not include air fares. This is dependent on availability of full financial support, but can relieve local sites from many trial related tasks. This may attract more sites to participate, provide a

smoother process of obtaining ethics approval, quicker trial start-up, higher inclusion rates and follow-up completeness.

Similar management strategies have been applied in the FAITH trial (Fixation using Alternative Implants for the Treatment of Hip fractures, NCT00761813). The FAITH trial is an international multicenter study initiated by the IHFRC (International Hip Fracture Research Collaborative).[21] The primary objective of this trial is to assess the impact of sliding hip screws versus cancellous screw fixation on rates of revision surgery at two years in elderly patients with femoral neck fractures. This trial has been launched in over 60 sites, predominantly situated in the Netherlands, Canada, and the US. All sites in the Netherlands are managed and visited by a single financed national trial coordinator. Most Canadian and US sites have individual local site coordinators and receive per patient payments. The aim of this study was to assess how these strategies affected performance of the FAITH trial.

Materials and Methods

Study Characteristics

In the Netherlands 14 hospitals participated in the FAITH trial. In Canada 11 hospitals participated, and in the US 29. Besides patient enrolment, sites were also required to register all patients that were excluded or missed for inclusion.

In the period before the trial started 26 of the participating Dutch, Canadian and US sites started prospective screening for patients during a short defined period to explore the amount and rate of potential inclusions that could be expected from each site. The results of this prospective screening study were used for the further planning of the definitive trial.

Two different strategies were applied for the organization and management of the FAITH trial in these participating countries. In the Netherlands the trial was coordinated and managed from a university hospital. One central, national trial coordinator was appointed upon obtaining adequate funding. This was a medical doctor working on her PhD project. This coordinator was responsible for all study related tasks at all fourteen participating sites. She arranged the process of ethics approval and the necessary documents for all sites, initiated study start-up, maintained communication with sites and the methods center, randomized all patients, and collected all follow-up data for 250 patients. During a period when study related tasks became too much to handle for a single person, she was assisted by the research team at the central coordinating site. There was no local research support at the participating sites. The coordinator travelled regularly to all participating sites, which were within a range of maximum 114 kilometers from the coordinating site. Participating sites were only responsible for patient selection. Sites received no payment; all funding was used for covering costs of the central trial coordination.

Most Canadian and US sites (located in various states ranging from Nova Scotia to British Columbia and from California to New York) were responsible themselves for all local study related tasks. The vast majority of these sites have individual, local, research assistants that take care of these tasks for the FAITH trial, as well as for other trials in that hospital. As compensation these sites receive per patient payment. In these countries there was no central, national trial coordinator.

All countries were supervised by the FAITH trial central methods center and steering committee. In order to monitor progress and to keep participating sites focused, there was contact between the methods center and the Dutch central coordinator, Canadian and US local principal investigators on a weekly base. The Dutch central coordinator had weekly contact with the participating sites and all sites received monthly newsletters showing the progress of the trial.

Data

Data related to trial initiation, organization, and performance were collected up to August 11, 2010. At this time patient recruitment was still ongoing in Canada and the US. Data were collected concerning:

- baseline characteristics; country, type of hospital (*i.e.*, university, non-university teaching, or non-university non-teaching), type of research coordinator (*i.e.*, not available, site-specific or provided for by central coordinating site);
- process of obtaining ethics approval; submission and approval date, number of submissions and type of revisions (*i.e.*, changes in wording or content of the informed consent form, changes in in- or exclusion criteria, changes in the wording or content of the study protocol, extra information on the study protocol and procedures, extra information on financial aspects, or request for additional documents);
- pre-trial screening period; screening start and stop date, total number of patients screened and number of eligible patients screened;
- trial period: trial start and (if applicable) stop dates, total number of included, excluded and missed patients that were registered, total number of patients that were missed for registration (for the Netherlands only), total amount of kilometers travelled by research coordinator and associated costs (for the Netherlands only), follow-up completeness.

Additional variables that were calculated from these data are described in Table 1.

Table 1. Additional variables calculated concerning the period of obtaining ethics approval and the screening and trial period

Variable	Calculation
Time necessary for ethics / IRB approval (days)	a – b
Time between ethics / IRB approval and start trial (days)	c – a
Screening period (days)	f – e
Enrolment / trial period (days)	d – c
Total number of patients in screening period (n per month)	g / (f – e)
Number of eligible patients in screening period (n per month)	h / (f – e)
Proportion eligible patients of total in screening period (%)	(h / g) * 100
Total number of patients per month in trial period (n per month)	(i + j) / (d – c)
Number of inclusions in trial period (n per month)	i / (d – c)
Proportion inclusions of total in trial period (%)	(i / (i + j)) * 100
Proportion patients that were missed for registration in trial period of total (%)	(k / (i + j + k)) * 100
Rate of total number of patients per month in trial period versus screening period	((i + j) / (d – c)) / (g / (f – e))
Rate of number of inclusions / eligible patients per month in trial period versus screening period	(i / (d – c)) / (h / (f – e))
Rate of percentage inclusions / eligible patients per month in trial period versus screening period	((i / (i + j) * 100) / ((h / g) * 100)

a, ethics / IRB approval date; b, ethics / IRB submission date; c, trial start date; d, trial stop date; e, screening start date; f, screening stop date; g, total number of patients screened; h, number of eligible patients screened; i, number of inclusions; j, number of excluded or missed patients that were registered; k, number of patients that were missed for registration.

Data Analysis

All analyses were conducted using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA). Data from the three countries (the Netherlands, Canada and US) were compared. The choice to compare these three countries was made because of the differences in trial management between the Netherlands and Canada/US described above. Comparing these countries separately also allowed the possibility to study country related differences that may affect trial performance, independent from the trial management strategy chosen. Continuous variables are presented as median with interquartile ranges. Categorical variables are presented as number (percentage). Continuous variables were compared with the Kruskal-Wallis Analysis of Variance (ANOVA). Post-hoc pair wise comparisons were performed using the Mann–Whitney U-test. Categorical variables were compared with the Chi-squared test. A P-value <0.05 (two-sided) was taken as threshold of statistical significance.

Results

Characteristics of participating sites

The type of hospitals participating was similar for the Netherlands (NL), Canada (CA) and the US (Table 2). All sites in the Netherlands were centrally coordinated, whereas local site coordination was available at 72.7% of Canadian sites and 96.6% of US sites.

Table 2. Characteristics of countries participating in the FAITH trial

	NL (N = 14)	**CA (N = 11)**	**US (N = 29)**	**P-value**
Type of hospital				
University	4 (28.6)	9 (81.8)	16 (55.2)	0.051
Non-university teaching	10 (71.4)	2 (18.2)	11 (37.9)	
Non-university non-teaching	0 (0.0)	0 (0.0)	2 (6.9)	
Trial coordinator				
Not available	0 (0.0)	0 (0.0)	1 (3.4)	<0.001
Available at site	0 (0.0)	8 (72.7)	28 (96.6)	
Provided by central coordinating site	14 (100.0)	3 (27.3)	0 (0.0)	

NL, the Netherlands; CA, Canada; US, United States.
Numbers in the headers represent the number of sites participating per country.
Data are presented as numbers with percentage between brackets. Statistics were calculated using the Chi-squared test.

Process of obtaining ethics / IRB approval

The time necessary for ethics / IRB approval was significantly longer in the Netherlands (median 104 days) than in Canada (median 55 days) and the US (median 53 days; p = 0.027; Table 3). For all countries the median number of submissions requested by the ethics committee was one. However, due to the differences in data distribution and skewness there was still a significant difference in requested submissions between NL (P25–P75 0.0–1.0) and the US (P25–P75 1.0–3.0) (p = 0.014). The type of revisions requested did not differ between the countries; the vast majority concerned wording and content of the informed consent form.

Pre-trial screening period

Of the currently participating FAITH sites four Dutch, eight Canadian, and fourteen US sites also took part in the pre-trial prospective screening period. The duration of the screening period did not differ significantly between groups (Table 4). The number of patients screened per site was least in the Netherlands with six patients in total and 3.3 patients per month. Forecasted total number of patients was highest for Canadian sites with 15 patients per site in total and 7.5 per month (p = 0.006 and p = 0.016). Other variables, concerning the amount and proportion of eligible patients screened, were not significantly different between countries.

Table 3. Data concerning the process of obtaining ethics / IRB approval of countries participating in the FAITH trial

	NL (N = 14)	CA (N = 11)	US (N = 19)	P-value
Time necessary for ethics / IRB approval[1] (days)	104 (74-135)	55 (27 – 77)	53 (44 – 105)	0.027[+ a]
Revision rounds[1]	1 (0.0 – 1.0)	1 (0.8 – 1.0)	1 (1.0 – 3.0)	0.014[+ b]
Type of revisions requested:				
Wording of IC Form[2]	6 (42.9)	5 (50.0)	12 (66.7)	0.382[++]
Content of IC Form[2]	6 (42.9)	5 (50.0)	8 (44.4)	0.938[++]
In- or exclusion criteria[2]	0 (0.0)	1 (10.0)	1 (5.3)	0.511[++]
Wording of study protocol[2]	0 (0.0)	1 (10.0)	0 (0.0)	0.185[++]
Content of study protocol[2]	1 (7.1)	2 (20.0)	1 (5.3)	0.406[++]
Additional information in study protocol / procedures[2]	5 (35.7)	3 (30.0)	7 (36.8)	0.932[++]
Financial aspects – Request for extra information[2]	0 (0.0)	1 (10.0)	3 (15.8)	0.303[++]
Request additional documents[2]	2 (14.3)	0 (0.0)	3 (15.8)	0.421[++]

NL, the Netherlands; CA, Canada; US, United States.
Numbers in the headers represent the number of sites per country for which data were available.
IC, informed consent form.
[1] Data are presented as median with P_{25}-P_{75} given between brackets. [2] Data are presented as number with percentages.
[+] Kruskal-Wallis ANOVA, [++] Chi-squared test
Post-hoc pair wise comparisons were performed using the Mann-Whitney U-test: [a] Statistical significance was reached when comparing NL vs. CA (p = 0.025), and NL vs. US (p = 0.019), CA vs. US: not significant.
[b] Statistical significance was reached when comparing NL vs. US (p = 0.007), other groups: not significant

Table 4. Data concerning the pre-trial screening period of countries participating in the FAITH trial

	NL (N = 4)	CA (N = 8)	US (N = 14)	P-value
Screening period (days)	55 (51 – 92)	60 (56 – 74)	50 (20 – 69)	0.121
Eligible patients (N)	4 (3 – 6)	4 (1 – 10)	3 (1 – 6)	0.571
Total patients (N)	6 (6 – 9)	15 (15 – 34)	6 (5 – 11)	0.006[a]
Eligible patients (N per month)	2.0 (1.7 – 2.4)	1.5 (0.7 – 4.1)	2.2 (1.1 – 5.0)	0.786
Total patients (N per month)	3.3 (3.0 – 3.6)	7.5 (5.6 – 17.4)	5.0 (3.1 – 8.2)	0.016[b]
Proportion eligible patients (% of total)	63 (53 – 67)	14 (10 – 40)	48 (29 – 71)	0.062

NL, the Netherlands; CA, Canada; US, United States.
Numbers in the headers represent the number of sites per country that data were available for.
Data are presented as median with P_{25}-P_{75} given between brackets.
Statistics were calculated using the Kruskal-Wallis ANOVA.
Post-hoc pair wise comparisons were performed using Mann-Whitney U-test: [a] Statistical significance was reached when comparing NL vs. CA (p = 0.009), and CA vs. USA (p = 0.004), NL vs. USA: not significant. [b] Statistical significance was reached when comparing NL vs. CA (p = 0.007), other groups: not significant.

Trial period

Dutch hospitals started enrolment in the period between February 2008 and October 2008. In August 2009 the national goal of enrolling 250 patients was achieved. Canadian hospitals started enrolment between March 2008 and June 2010. In the US hospitals started enrolment between February 2009 and September 2010. In Canada and the US enrolment is still ongoing.

The time necessary for trial start-up was defined as the time between obtained ethics approval and the actual trial start up. With a median of 41 days, trial start-up was fastest for the Netherlands. Trial start-up took more than five times longer for Canada (median 232 days; $p = 0.027$; Table 5). Because the median enrolment period was statistically significantly longer for the US than for the Netherlands (median 283 vs. 423 days, respectively, $p = 0.001$), crude numbers were also calculated per month. The total number of patients seen per month in the trial period was similar in all countries; however, the inclusion rate in the Dutch sites per month was more than three times higher than in the US sites, and more than seven times higher compared with Canadian sites (1.03 patients per month vs. 0.31 and 0.14, respectively, $p < 0.001$). Inclusion progression of all countries is also shown in Figure 1. Similar differences were seen when comparing the proportion inclusions of the total patient group. In Dutch sites 34.4% of the patients were included vs. 16.7% in US sites and 3.93% in Canadian sites ($p = 0.001$). These numbers may however be influenced by the varying screening compliance in all countries. For example, sites screening all hip fractures would certainly have greater screening failure rates than those sites screening only those hip fractures that were deemed treatable by internal fixation.

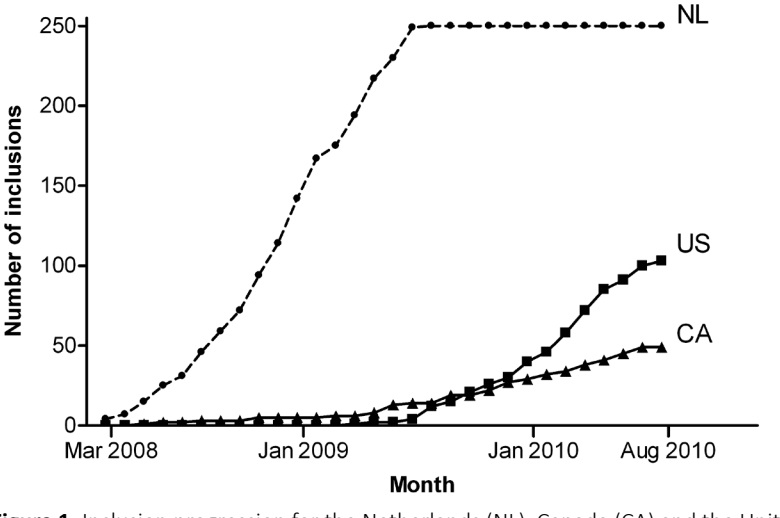

Figure 1. Inclusion progression for the Netherlands (NL), Canada (CA) and the United States (US)

Table 5. Data concerning the trial period of countries participating in the FAITH trial

	NL (N = 14)	CA (N = 11)	US (N = 29)	P-value
Time between ethics approval and start trial (days)	41 (10 – 139)	232 (98 – 423)	87 (45 – 255)	0.027[a]
Enrolment period (days)	423 (381 – 509)	482 (267 – 663)	283 (142 – 360)	0.001[b]
Inclusions	13 (7 – 27)	3 (0 – 5)	3 (1 – 6)	<0.001[c]
Registered patients	23 (12 – 36)	54 (3 – 75)	16 (5 – 27)	0.060
Patients missed for registration[1]	35 (10 – 81)	Unknown	Unknown	
Inclusions (n per month)	1.03 (0.43 – 2.21)	0.14 (0.00 – 0.28)	0.31 (0.09 – 0.62)	<0.001[d]
Total patients (n per month)	2.49 (1.60 – 3.64)	2.76 (0.60 – 8.75)	1.96 (1.11 – 3.75)	0.574
Proportion inclusions (% of total)	34.4 (23.8 – 62.6)	3.93 (0.00 – 13.2)	16.7 (2.50 – 31.3)	0.001[e]
Proportion patients that were missed for registration of total[1] (%)	57.4 (32.2 – 65.2)	Unknown	Unknown	
Completed follow-ups (%)	82.6 (80.0 – 84.6)	83.5 (72.7 – 95.2)	70.0 (60.0 – 88.1)	0.217
Follow-ups in window (%)	77.1 (71.0 – 82.2)	85.9 (81.0 – 95.0)	85.7 (70.0 – 100.0)	0.073

NL, the Netherlands; CA, Canada; US, United States.
Numbers in the headers represent the number of sites per country that data were available for.
Data are presented as median with P_{25}-P_{75} given between brackets.
Statistics were calculated using the Kruskal-Wallis ANOVA.
[1] Data available for NL only.
Post-hoc pair wise comparisons were performed using a Mann-Whitney U-test: [a] Statistical significance was reached when comparing NL vs. CA ($p = 0.010$), other groups: not significant. [b] Statistical significance was reached when comparing NL vs. US ($p < 0.001$), other groups: not significant. [c] Statistical significance was reached when comparing NL vs. CA ($p = 0.002$) and NL vs. US ($p < 0.001$), CA vs. US: not significant. [d] Statistical significance was reached when comparing NL vs. CA ($p = 0.001$) and NL vs. US ($p = 0.001$), CA vs. US: not significant. [e] Statistical significance was reached when comparing NL vs. CA ($p < 0.001$) and NL vs. US ($p = 0.009$), CA vs. US: not significant.

For sites in the Netherlands data were extracted from hospital records in order to check for omissions in patient registrations during the trial. A median of 35 excluded and missed patients (P25-P75 10-81) were not registered per site, despite clear instructions to participating sites that this was required for the trial. This represented 57.4% of the total amount of patients seen during the trial period. These data were not available for the other countries.

Follow-up data were collected at eight time points, four times in clinic and four times by telephone. The percentage completed follow-ups were calculated for all time points and the overall percentage completed follow-ups was computed. The median overall percentage completed follow-ups was 70% in Canada, and exceeded 80% in the Netherlands and US. No statistically significant differences were found between countries (Table 5). The median percentage of follow-ups that were completed within the predefined acceptable time window was 77% in the Netherlands, and 86% in Canada and the US. Again, this was not statistically significantly different (Table 5).

During this study, the central trial coordinator in the Netherlands travelled 28,842 kilometers in order to visit all fourteen participating sites for trial start-up, enrolment, and data collection in clinic. This resulted in € 9,771 total travel costs.

Pre-trial screening period versus trial period

Pre-trial screening data regarding eligible patients were compared with the actual inclusion rates and percentages in the trial period, to study the value of pre-trial screening data. An overview of the calculated variables is shown in Table 1. Inclusion rates in the trial were much lower than expected from the screening period: a decline of 67% (P25-P75 42–83) was noted for sites in the Netherlands versus a decline of 92% (P25-P75 78–100) for US and 93% (P25-P75 68–100) for Canadian sites (p = 0.154; Figure 2). The total number of patients seen in the trial period versus the screening period also displayed a decline: 41% less (P25-P75 -2–62) for the Netherlands versus 52% (P25-P75 9–88) for Canada and 69% (P25-P75 35–81) for the US (p = 0.477). Consequently, the proportion inclusions of the total patient group also decreased: 48% decrease (P25-P75 14–69) for sites in the Netherlands versus 83% (P25-P75 39–100) for Canadian sites and 83% (P25-P75 56–100) for US sites (p = 0.091).

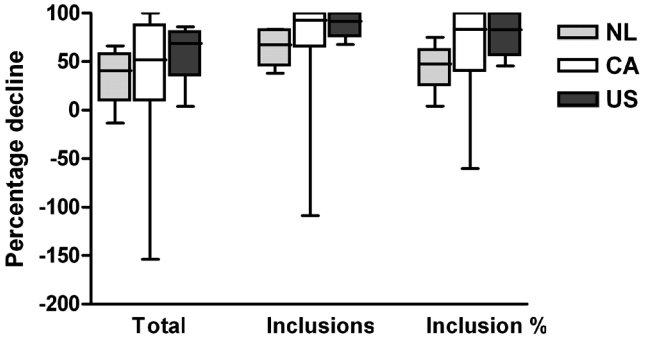

Figure 2. The percentage decline in total number of patients seen per month, number of inclusions per month and percentage inclusions of total number of patients, during the trial period in comparison with the pre-trial screening period. To calculate this percentage decline, the total number of patients seen in the trial period was divided by the total number of patients seen in the pre-screening trial period. Similar calculations were made for the number of inclusions per month and the inclusion percentage. These rates (a) were transformed to a percentage decline (b) using the following formula: b = (1-a) * 100%. This figure therefore shows that for all variables there were fewer patients during the trial period compared with the pre-trial screening period in all countries.
NL, the Netherlands; CA, Canada; US, United States.

Discussion

In this study, trial progression in the Netherlands, where a central trial coordinator managed most tasks for multiple centers in a restricted geographical area, was better than in Canada and the US, where local research assistants were appointed at individual sites. The central trial coordinator system was associated with a shorter trial start-up time, higher inclusion rate, and a higher inclusion percentage. Collection of follow-up data was equally good in both systems.

The process of obtaining ethics approval can be time-consuming and stressful and may yield diverse responses from ethics committees.[9-13] For the FAITH trial, obtaining ethics approval took longer in the Netherlands than in Canada or the US. This may have been influenced by the time that the trial coordinator or sites needed to assemble forms for the ethics committee. Ethics submissions may have taken longer in the Netherlands at the very start of the trial, when there was no central trial coordinator yet. The longer approval process in the Netherlands may also have been caused by more inefficient medical ethics procedures.[10] In the Netherlands multicenter studies need approval from a central ethics committee that performs a full review of the study documents. Subsequently, ethics committees in participating sites should only advise on local feasibility. This two-step approach was aimed to simplify and shorten the ethics procedures for multicenter trials. It is nevertheless disputable if this goal is currently achieved.[10] In Canada and the US a single procedure for study review and approval is performed at all sites, which may turn out to be more efficient.

The number of resubmissions requested by the ethics committees was lower in the Netherlands, and can therefore not have contributed to the prolonged approval process. The availability of a central trial coordinator with detailed insight and knowledge on the study content could have prevented incorrect submissions in the Netherlands. In all countries remarks of the ethics committees mainly involved the informed consent form and extra information on the study protocol and procedures. Standardization of the ethics approval process is recommended as it may reduce the local differences in ethics approval terms.

The trial start-up period was statistically significantly shorter in the Netherlands (median 41 days) than in the US and Canada (87 and 232 days). In these latter two countries contract negotiations with participating sites had to take place during the trial start-up period, whereas this procedure was not applicable in the Netherlands. Furthermore, research assistants from Canada and the US frequently reported a long period between grant approval and official release of the funds. These aspects related to the per patient payment strategy applied in Canada and the US slowed the trial start-up process in these countries. In the Netherlands contract negotiations or per patient payments were unnecessary, as all tasks were performed by the central study coordinator, not resulting in delay. The assistance of the Dutch central trial coordinator in trial start-up activities (*e.g.* distributing study materials, giving start-up presentations) may also have contributed to a more efficient and speedy trial start-up.

Most influential to the differences in trial progression between the countries were the evident differences in inclusion rate and percentage, which were statistically significantly higher for sites in the Netherlands. The availability of the central trial coordinator in the Netherlands made it possible for smaller, non-university sites without a local research infrastructure or coordinator to participate. These sites generally treat more patients from the targeted population (*i.e.*, femoral neck fracture patients) than the large university hospitals, but would normally not have been able or willing to participate in the trial, because they lack a local coordinator. Most of the principal investigators of these sites reported to be very motivated to enroll patients, as the (administrative) burden of participation was relatively low, thanks to the fact that the performance of follow-ups and other trial related tasks were adopted by the central trial coordinator. They declared that this was crucial in their decision to participate. This high devotion and lack of burdensome trial related tasks will probably have contributed to a good inclusion rate. Therefore, the availability of a central trial coordinator can contribute to a fast enrolment, both directly, by motivating local principal investigators to participate and enroll because of the low (administrative) burden of participation, and indirectly, by enabling high-volume hospitals without a local research network to participate. However, differences in accrual between countries may also have been affected by the known intercultural differences in preferred treatments for femoral neck fractures.[22] North American surgeons may have considered less femoral neck fracture patients suitable for internal fixation than Dutch surgeons do, as they are less committed to internal fixation as a preferred treatment. Moreover, surgeons from the US and Canada reported at investigator meetings that North American patients may be less lenient to participate in trials and that they experienced problems at obtaining informed consent.[23] Within the countries, higher accrual was also associated with a large target population, dedicated and compliant principal investigators, and low study related workload for participating surgeons. These are important aspects to pursue when planning a multicenter randomized controlled trial, and can be facilitated by appointing a central trial coordinator.

Comparison of the pre-trial prospective screening data with the actual trial data showed an obvious discrepancy in all countries. It is known that participating surgeons tend to overestimate enrolment numbers based upon a pre-trial screening period.[24] In this study accrual was also much lower than expected from the screening period. The use of pre-trial screening can therefore be debated. However, it may be useful to indicate good dedication to participate and help raise awareness for the upcoming study in potential sites. If a pre-trial screening is deemed necessary, a retrospective approach is recommended, as it is easier and results in similar estimated numbers, compared with a prospective approach.[24]

The percentage completed follow-ups was not affected by the availability of a central trial coordinator and was between 70% and 84% for all countries. Follow-ups did seem to be completed within the window a bit less in the Netherlands, although not statistically

significant. This was a result of the limitations that we experienced from the central trial coordinator approach. Usefulness of this approach will decrease with an increased sample size and an increased distance between sites. A single person can only manage a certain maximum number of sites and patients. Similarly, there is a maximum to the distance that can be traveled per day. In our study, a single study coordinator to manage 14 sites and 250 patients seemed somewhat limited. The study coordinator had to complete eight follow-ups per patient (four clinical and four telephonic), in 14 sites that were maximum 140 km. apart (maximum 2 hours travel time), resulting in an average of almost 1,000 km traveled per week. In these circumstances it was not always feasible to manage all follow-ups. We feel that it would have been optimal to have one coordinator following a maximum number of 200 patients, in our study. It is also important to have a supporting research team available for assistance if work pressure gets too high for a single person. The central coordinator approach is feasible within European countries, as well as within American/Canadian states.

Finally, a central coordinator may also contribute to the impartiality of the collected data and may prevent biases that could be introduced if the local coordinators/participating doctors are also the treating physician. Obviously, this could not be analyzed or proven in this study.

Obviously, this study has its limitations. Many of the results of this study were multifactorially influenced. Not all differences between countries can therefore be attributed to the difference in trial management system. If the two models (*i.e,* central management and local management) would have been conducted equally in each of the countries, bias due to country-specific conditions could have been ruled out. This was however impossible in the current study. Nevertheless, the availability of the central coordinator has certainly contributed to the speedier trial start-up, high enrollment rates and complete follow-up. Also, the limited number of sites available for data assemblage (especially for the screening period) and the fact that not all data were collected prospectively may have introduced some bias.

Conclusions

In summary, trial performance can be influenced by the management strategy chosen. This study shows that the appointment of a central financed trial coordinator to manage all trial related tasks is a feasible alternative for the more traditional approach of appointing trial related tasks to local research assistants at participating sites. Taking important circumstances such as available budget, sample size, and geographical area into account, a central trial coordinator approach can add to the success of a multicenter randomized trial. A central coordinator should be considered when studying injuries that occur more frequently in smaller regional hospitals (without a local research coordinator). It will enable these sites to participate in randomized controlled trials, resulting in an enhanced enrolment rate. It

should also be considered when the targeted principal investigators are unable to participate due to the (administrative) burden of participation. However, a central coordinator should only be considered for multiple sites in a restricted geographical area. Depending upon the geographical spread of the sites and the frequency of follow-up a careful estimation should be made of the amount of patients and sites that can be managed by a single coordinator.

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Chapter 3

Surviving a Site Audit: Tips for Good Clinical Practice in an Implant Trial

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Abstract

The number of clinical trials involving implants for trauma and orthopedic surgery is increasing. The International Conference of Harmonization-Good Clinical Practice (ICH-GCP) guideline has been developed in order to assure that the rights, safety, and well-being of trial subjects (*i.e.*, patients) are protected. Not performing a trial according to legal requirements including this guideline is no longer acceptable, and trial audits are increasingly being performed as an independent quality check for data validity and credibility. This manuscript provides an overview of the Guideline for Good Clinical Practice in the context of conducting an implant trial in trauma and orthopedic surgery. As long as all guidelines are adequately adhered to and all paperwork is in order, there is no reason to fear a trial audit.

The principles of ICH-GCP

The ICH-GCP guideline, which has its origin in the Declaration of Helsinki, is an international ethical and scientific quality standard for the design, conduct, recording, and reporting of trials involving human subjects.[2,3] The guideline provides a unified standard for clinical research in the European Union, Japan and the United States, in order to facilitate mutual acceptance of clinical data by regulatory authorities in these jurisdictions.

The key principle of the ICH-GCP guideline is the ethical conduct of a trial.[2] No trial can be initiated before all foreseeable risks and inconveniences are weighted against the anticipated benefit for the individual trial subject and society. The safety and well-being of the trial subjects should always prevail over scientific interest.[2] Medical device GCP includes the following key items: (1) Appropriate clinical trial documentation as defined by ICH-GCP; (2) Medical Ethics Committee approval of the trial; (3) Ethics committee supervision and review of amendments and adverse events; (4) Written clinical trial study report about the study outcome. If applicable, competent authority approval should also be obtained.

Designing the trial and writing the study protocol

Clinical trials should be scientifically sound, and described in a clear, detailed protocol.[2] The protocol should provide detailed information on the rationale, aims, objectives, design, proposed analyses, methodologies, data analyses, and conduct of the trial. Table 1 provides an overview of key topics to be mentioned in the protocol. Local authorities may also require that the applicable ethics issues are adequately addressed in the protocol.

Table 1. Content of the trial protocol

• Title of the project
• Names, qualifications and addresses of the sponsor (*i.e.*, trial initiator)
• Justification and rationale of the trial, including literature overview
• Objectives of the trial, including testable hypothesis
• Inclusion and exclusion criteria
• Details on randomization, blinding and treatment allocation
• Definition of the interventional procedures
• Details on the implant tested
• Anticipated adverse events and related risks associated with the implant
• Definition of perioperative care, after-treatment and any other trial-specific treatments*
• Detailed overview of outcome assessment, including justification
• Detailed list of data to be collected, including procedures how to collect these
• Required sample size, including statistical justification
• Definition of statistical methodologies to be applied
• Details on handling and storage of data and documents
• Details on public disclosure and publication
• Detailed list of literature references

* Only if applicable

All relevant literature related to the efficacy and safety of the implant should be summarized in the protocol. The best approach for assessing available literature data is by performing a systematic review and/or meta-analysis. Commonly used electronic databases include MEDLINE, EMBASE and CINAHL. Depending on the topic, recent systematic reviews may already be available in the Cochrane library. The conduct of a meta-analysis helps to systematically appraise the available evidence, and will provide guidance in formulating a testable research question for the trial.

In surgical study protocols attention should also be paid to surgeon related aspects. The individual skills and habits of the orthopedic trauma surgeon participating in a clinical trial may influence the outcome of the trial. Therefore, it may be important to standardize key elements of the intervention for both the treatment group(s) and the control group in order to reduce bias due to variation in techniques and skills of participating surgeons.

There are several options for reducing technique-associated bias, each with related advantages and disadvantages. These options include: (1) all surgeries are being done by the same surgeon; (2) obliged teaching sessions prior to the trial; (3) auditing surgical performance throughout the trial; and (4) stratifying patients by surgeon at the time of randomization. For specific interventions it may also be better to determine a priori how may procedures each participating surgeon should have performed in his/her entire career and/or in the last year prior to trial startup.

Similar to the standardization of surgical and technique associated factors, guidelines regarding peri-operative care (*e.g.*, thromboprophylaxis, antibiotic prophylaxis, optimization for surgery, pain medication) and after-treatment (*e.g.*, physical therapy) should be specified in the protocol if relevant for the trial.

Availability of experienced surgeons is critical when it comes to the ability to enroll patients at any time. Any site participating in a trial should have a team with adequate skills, expertise and equipment available for participation. Trials involving acute traumatic injuries may require the prompt availability of a skilled surgical team.

Other key aspects of a methodologically sound study design are randomization, allocation concealment, and blinding.[4-8] Randomization ensures that both known and unknown prognostic factors are equally distributed in the treatment and control group. Allocation concealment prevents undermining of random, unpredictable assignment sequences resulting in overestimated treatment effects. [4,8] In surgical trials, blinding of patients and surgeons may not be feasible. Blinding of outcome assessors should be aimed at as much as possible, as treatment effects are known to be over-estimated in unblinded studies. [4,7,9,10] If applicable, one might consider blinding of radiographs by superimposing the implants used in either trial arm.[11] Blinding of the surgical site could be achieved by covering it with the same band-aid, regardless of the intervention.

It is becoming more common to publishing the trial protocol prior to or immediately following trial startup. Early publishing of the trial protocol may lead to higher protocol adherence, and at the same time may set a higher threshold for any post-hoc protocol revisions and amendments. In the future, more scientific journals may also request submission of the trial protocol together with the final manuscript in order to identify protocol deviations.

Ethics approval and trial registration

Clinical trials are closely supervised by legal authorities. All clinical trials that involve an intervention on patients must be approved by a supervising ethics review committee before permission is granted to run the trial. After receiving this permission, the trial should be conducted in compliance with ICH-GCP, strictly following the study protocol.

An ethics review committee is an independent body of medical professionals, and lay members. Usually this committee is called a medical research ethics committee (MREC or EC), or Institutional Review Board (IRB) for the US. An independent ethics committee can be consulted if the local investigator's hospital or institution has no MREC or IRB. The legal status, constitution, and responsibilities of ethics committees may differ from country to country.

The mandate of the ethics review committee is to safeguard the rights, safety, and well-being of all research participants. Ethics committees review the study protocol, the case report forms, the study budget and trial participant payment, the consent form, and any other study documentation in order to ensure that the trial is justified, safe, that the patients are properly informed about the research, and that adequate facilities and resources are available. Table 2 provides an overview of trial documents to be reviewed by the ethics committee. They may request changes in study procedures or in the explanations given to the patient (*e.g.*, patient information brochure or consent form).

Table 2. Overview of trial documents to be reviewed by the ethics committee

• Application form, including names and qualifications of participating surgeons
• Study protocol
• Investigational brochure and other documentation related to the trial (*e.g.*, Standard Operations Manual)*
• Information sheet for research participants
• Consent Form for research participants and/or their legal representative
• Data collection booklets/Case Report Forms/questionnaires
• Promotion material (*i.e.* study posters or pocket cards)
• Details on radiology and/or toxicology safety
• Details on payment to trial participants
• Letters of agreement and/or contract with sponsor*
• Up-to-date, dated and signed Curriculum vitae (CV) of the principal investigator, all co-investigators and independent physician
• Trial termination criteria*

* Only if applicable

In the US and most European countries, the local ethics review committee must certify that site (principal) investigators and their staff have adequate knowledge on ICH-GCP before they can conduct clinical trials. Attending an ICH-GCP course is often compulsory for the principal investigator.

For multicenter trials, one MREC or IRB will act as primary, central ethics review committee. They perform a full review of the study documents and should approve the trial prior to its startup. Local MRECs or IRBs should only advice on feasibility of the trial at that particular site. International trials require a central ethics review committee in every participating country.

Once the trial has been approved by the ethics review committee, it is necessary to continue to communicate regularly with the MREC or IRB. Investigators are obliged to submit an annual update report on the progress of the study and any new safety information related to the study. Also, all amendments to the protocol, consent form, and case report forms must be promptly reported. Amended documents cannot be implemented before approval of the ethics review committee has been obtained.

In addition to ethics approval, legislation in some countries requires registration of trials in a public trial register. An overview of primary registries that meet the requirements of the International Committee on Medical Journal Editors (ICMJE) is given in Table 3.

Table 3. Primary Registries in the WHO Registry Network

Registry	Website
Australian New Zealand Clinical Trials Registry (ANZCTR)	http://www.anzctr.org.au/
Chinese Clinical Trial Register (ChiCTR)	http://www.chictr.org/
Clinical Trials Registry- India (CTRI)	http://www.ctri.in/Clinicaltrials/index.jsp
German Clinical Trials Register (DRKS)	http://www.germanctr.de/
Iranian Registry of Clinical Trials (IRCT)	http://www.irct.ir/
ISRCTN.org	http://www.isrctn.org/
Japan Primary Registries Network (JPRN)	http://www.isrctn.org/
The Netherlands National Trial Register (NTR)	http://www.trialregister.nl/trialreg/index.asp
Pan African Clinical Trial Registry (PACTR)	http://www.pactr.org/
Sri Lanka Clinical Trials Registry (SLCTR)	http://www.slctr.lk/

Primary registries in the WHO Registry Network meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration. Primary Registries meet the requirements of the ICMJE (International Committee on Medical Journal Editors) are listed, along with their websites.
(Source: http://www.who.int/ictrp/network/primary/en/index.html).

Informed consent and recruitment

Ensuring informed consent from the participants is a major cornerstone of ethical human subject research. In compliance with ICH-GCP guidelines, every trial subject should give his/her informed consent prior to clinical trial participation.[3] Consent is considered 'informed' when given by a person who understands the purpose and the nature of research, what is required from the participant and what may be the potential benefits and risks resulting from the study. If the patient is unable to consent for him/herself, researchers can seek consent from the patient's legally authorized representative. Who is entitled to act as legal representative may differ between countries, depending on local legislation.

If limited numbers of trial subjects are to be expected at a single site, it may be preferable to choose for a multicenter approach, thereby reducing the time needed for trial subject enrolment. As a consequence, the process of obtaining MREC or IRB approval will take more time to complete, as local feasibility of the trial needs to be tested by a local ethics review committee at each participating site.

Adverse event reporting

If during the trial an adverse event is encountered, this should be reported to the local MREC or IRB. An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a trial-specific product (*e.g.*, implant, medical device or pharmaceutical product) and which does not necessarily have a causal relationship with this treatment.[3] A serious adverse event is an adverse event which results in death, is life-threatening, requires in-patients hospitalization (or prolongs existing hospitalization), results in persistent or significant disability of incapacity, or is a congenital anomaly or birth defect.[3] A non-serious adverse event is any adverse event that does not meet the criteria of a serious adverse event. Many review boards require serious adverse events to be reported within 24 hours and non-serious adverse events to be reported within 48 hours, in compliance with ICH-GCP guidelines. If applicable, adverse events should also be reported to the data safety and monitoring board.

The research team

The medical care given to, and medical decisions made on behalf of trial subjects should always be the responsibility of a qualified physician.[3] However, the overall conduct of the trial and the trial-related activities may involve a dedicated research team. Each individual in this team should be qualified by education, training, and experience to perform his or her respective tasks.[3] A single center trial requires a different team than a large, international trial

involving multiple sites per country. Multicenter trials usually have a central project office or methods center that coordinates and overseas the trial. Requirements and responsibilities of key persons and groups within the team are given below.

Site principal investigators and site investigators

If a participating clinical site has more than one surgeon enrolling patients into the trial, one investigator from each site should be designated as the site principal investigator (PI). The PI is the medical practitioner or licensed medically qualified person conducting the study in accordance with the protocol. The site PI serves as the primary contact for the sponsor or central methods center, and is responsible for all communication with the local MREC or IRB. The site PI should also ensure correct documentation in case report forms and patient hospital records to enable source data verification. In multicenter trials, the site PI also attends investigator meetings and conference calls regarding the trial.

A site PI may appoint any number of co-investigators who are given the responsibility to actually conduct the trial as defined in the clinical investigation plan. The site investigators are responsible for enrolling patients into the trial, following the study protocol, and following patients according to the study protocol.

In addition to the site investigators, the site PI may also appoint a dedicated clinical research coordinator to manage the day-to-day trial activities at the clinical sites. These include regular communication with the local ethics committee, assisting with the patient enrolment, completing case report forms, scheduling patient follow-up appointments, and entering data into a database or submitting data to the central methods center. The clinical research coordinator and the site PI work closely together to ensure compliance and data quality.

Sponsor

The sponsor is the organization that has initiated the trial. This could be a medical industrial company or a hospital. The sponsor and the local site PIs are jointly responsible for writing a site-specific patient information brochure and informed consent form that accurately informs the potential subjects about the true risks and potential benefits of participating in the study, while at the same time presenting the material as briefly as possible and in ordinary language.

Throughout the clinical trial, the sponsor is responsible for: (1) accurately informing the local site (principal) investigators about any relevant news on the trial; (2) monitoring the results of the study as they come in from the various sites, as the trial proceeds; and (3) collecting adverse event reports from all site investigators in the study, and for informing all the investigators of the sponsor's judgment as to whether or not these adverse events were related to the study treatment.

Steering Committee

The sponsor may appoint a Steering Committee that will be responsible for the overall design and conduct of a trial. This committee consists of the principal investigator(s), the biostatistician and trial methodologist, and other key investigators. It communicates with the Data Monitoring Committee, the Central Adjudication Committee, and the site PIs. At the completion of the trial, the Steering Committee maintains responsibility for the final data analysis and publication.[12]

Data monitoring committee (DMC)

In larger clinical trials, a sponsor will use the services of a DMC, known in the U.S. as a Data Safety Monitoring Board.[12] This is an independent group of health care professionals who are completely independent of the investigators and who have no financial, scientific, or other conflict of interest with the trial. The DMC members should have adequate expertise in clinical trial methodology, biostatistics, and regulatory guidelines like ICH-GCP. The DMC reviews unblinded data related to the conduct of the study (*e.g.*, recruitment rates, non-compliance, and protocol violations), carries out evaluations of serious unanticipated adverse events, evaluates pre-planned interim analyses for efficacy, safety, and the triggering of statistical warning rules. The DMC has the power to recommend termination of the study based on their review.

Central Adjudication Committee (CAC)

The CAC is designated to review important study end-points reported by the trial investigators to determine if they meet protocol-specified criteria. Site investigators should provide them with all relevant information such as X-rays, surgical reports, and clinical notes. If feasible, the CAC should be blinded to treatment allocation where ever possible in order to reduce bias and random error in determining outcome events.[4,7,12] This committee is optional and can be beneficial in surgical trials, in which the intervention(s) cannot be blinded.

Data management and trial monitoring

Following initiation of a clinical trial, progress and quality of the collected data should be monitored in detail. The purposes of clinical trial monitoring is to verify that the rights and well-being of human subjects are protected, to verify that the reported clinical trial data are accurate, complete, and verifiable from source documents, and to verify that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH-GCP, and with the applicable regulatory requirement(s).

Although the sponsor holds the overall responsibility of the trial, it is the responsibility of the site PI and the site investigator(s) to provide complete and high-quality data. A sponsor

may appoint monitors to oversee the conduct of the trial or hire a Contract Research Organization (CRO) for that purpose. The monitor continuously conducts the in-process quality control for the trial, checks the performance of the trial and its compliance with the overall legal requirements and ICH-GCP. The monitor represents the sponsor, periodically visits the trial sites and reviews the data through source data verification (*i.e.*, reviewing the collected data against the medical records and reports pertaining to the trial subject).

ICH-GCP guidelines dictate that all clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. [3] All data concerning a trial participant should be stored in a folder, in which each document should have the subject's unique identifier. In compliance with regulatory requirements regarding privacy and confidentiality protection, subjects should be given a unique identification number.[3] A common numbering system is a combination of the trial acronym (or protocol number), followed by the site number and subject number.

Data collection may be challenging, both in single as in multicenter trials. Coordinating centers increasingly use centralized computer data collection systems that can be fax-based or Internet-based.[1,13] Data should be checked for missing information, implausible data, and inconsistencies at an early stage. Any problem encountered should be corrected as early as possible. This is primarily the task of the local research coordinator. Failure to resolve problems urgently will violate the ICH-GCP guideline and can result in termination of the trial by the authorities as a worst-case scenario.

Regulatory device trials

Regulatory device trials allow for the clinical evaluation of (new) medical devices, determining whether or not they can be safely and effectively used in patient care.[14]

In the US, the Food and Drug Administration (FDA) must give approval to all clinical trials involving new medical devices that pose a significant risk to patients. Depending on the assigned level of risk (*i.e.*, class I, II, III), a clinical trial involving an approved medical device for a new indication not covered by the initial marketing approval may also require FDA approval.[15] In the EU, all medical devices must be identified with the CE (Conformité Européenne; in English European Conformity) mark. There are numerous 'Agreements on Mutual Recognition of Conformity Assessment' between the EU and other countries such as the USA, Japan, Canada, Australia, New Zealand and Israel. Regulatory trials must function in compliance with governmental regulations. Legislation may vary considerably between countries.

Participation in a regulatory trial is more complex and time-intensive than participating in a non-regulatory trial. Regulatory trials require an even stricter adherence to ICH-GCP. In practice, the administrative workload will be higher and details must be recorded, sometimes to the extreme.

Trial auditing

Following in-process quality checks by a trial monitor or DMC, auditing or inspection is the second line of defense for trial compliance. The ICH-GCP guideline defines an audit as a systematic and independent examination of trial-related activities and documents for industry-sponsored trials. An audit can be requested by the sponsor, but also by formal bodies such as the ethics committee. The aim of the audit is to ensure that trials are conducted in compliance with the trial protocol, the sponsor's standard operating procedures, and all applicable guidelines and regulatory requirements. In other words, auditing is critical in ensuring that the collected data is credible and reliable. Audits are conducted at the time of screening, halfway during the trial and at the trial closure.

Clinical trial audits are performed by regulatory authorities, trial sponsors, or organizations nominated by the trial sponsor.[3] The regulatory authorities in the United States and European Union perform audits of the sponsor, manufacturing plants, and study sites. Study sites always receive advanced written notification of an audit, allowing them sufficient time to prepare for the audit. Auditing uses a structured agenda and clearly defined objectives. The auditor will provide a checklist of documents and data that should be available, along with a list of persons to be present during the audit.

Any issues identified that could result in major non-compliances should be properly addressed by the site PI immediately after they have been identified. Negative audit findings may vary in severity from deficiencies in essential trial documentation that can easily be rectified, to errors in consent procedures and investigator fraud. Serious discrepancies may lead to termination of a trial at a study site or legal proceedings against an investigator.

As audits can be very stressful for investigators, they need to be thoroughly prepared. Organizing training sessions or pre-investigational site visits may reveal any problems that might be encountered during the actual audit, and will enable the site PI the chance of a timely solution. As long as all members of the research team conduct the trial in agreement with ICH-GCP guidelines and other regulatory requirements, they have nothing to fear.

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Part II

Chapter 4

Adherence to a femoral neck fracture treatment guideline

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Abstract

Purpose: In 2007 the Dutch Surgical Society published a clinical practice guideline for the treatment of hip fracture patients, based on the best available international evidence at that time. We investigated to what extent treatment of femoral neck fracture patients in the Netherlands corresponded with these guidelines, and determined differences in patient characteristics between the treatment groups.

Methods: All femoral neck fracture patients treated in 14 hospitals between February 2008 and August 2009 were included. Patient characteristics, X-rays, and treatment data were collected retrospectively.

Results: From a total of 1250 included patients 59% had been treated with arthroplasty, 39% with internal fixation, and 2% with a non-operative treatment. While 74% of the treatment choices complied with the guideline, 12% did not. In 14% adherence could not be determined from the available data. Arthroplasty was preferred over internal fixation in elderly patients with severe comorbidity, pre-fracture osteoporosis and a displaced fracture, that were ambulatory with aids pre-fracture (odds ratio, OR 2.2-58.1). Sliding hip screws were preferred over cancellous screws in displaced fractures (OR 1.9).

Conclusions: Overall guideline adherence was good. Most deviations concerned treatment of elderly patients with a displaced fracture, and implant use in internal fixation. Additional data on these issues, preferably at a higher scientific level of evidence, is needed in order to improve the guideline and to reinforce a more uniform treatment of these patients

Introduction

Hip fractures are associated with 30% mortality at one year and a profound temporary, sometimes permanent impairment of independence and quality of life.[1] Worldwide, 4.5 million people are disabled of hip fractures yearly, with an expected increase to 21 million persons living with a disability by 2040.[2,3] Approximately 50% of all hip fractures are intracapsular fractures of the femoral neck.[4] These can be treated with a non-operative treatment, internal fixation or arthroplasty.

In 2007 the Dutch Surgical Society (NVvH) published a guideline on the treatment of hip fracture patients.[5] This guideline provides a decision tree for the treatment of femoral neck fracture patients (Figure 1). Decisions are based upon evidence-based patient and fracture characteristics, that are relevant in the Netherlands as well as internationally.[4,6-12] The guideline reflects surgical guidelines and behavior in Europe, although the English guideline is more detailed, especially concerning arthroplasty.[13]

There is consensus that patients with undisplaced fractures should be treated with internal fixation.[4] Surgeons also agree that femoral neck fracture patients with arthrosis, rheumatoid arthritis, or a pathologic fracture should be treated with arthroplasty, as these conditions are contraindications for internal fixation. Surgeons agree that elderly *(i.e.*, >80 years old) with a displaced fracture should receive arthroplasty as well.

There is no clear consensus on the treatment of younger patients with a displaced fracture.[6,7,9,10,14-16] From meta-analyses it is known that internal fixation may lead to lower infection rates, less blood loss, a shorter operative time, and possibly a decrease in mortality rate. In contrast, arthroplasty significantly reduces the revision surgery rate.[9,10,17] Therefore, it is generally recommended that internal fixation can be used in patients with limited comorbidity and a low ASA-score (American Society of Anaesthesiologists), who are mobile, independent, and not cognitively disabled pre-fracture. Patients for whom the risk of revision surgery is considered too high should be treated with arthroplasty.

After the decision for arthroplasty or internal fixation has been made, the type of prosthesis (*i.e.*, hemi-arthroplasty or total hip arthroplasty) or internal fixation (most commonly sliding hip screw or cancellous screws) has to be selected. Again, there is no consensus and surgical preference may play a role.[6,18-22]

In summary, for some patient groups there is still a need to define if they will benefit from a specific treatment.[10] The guideline provided the best available evidence when developed in 2007. As it cannot provide level I evidence for all patients, we anticipated that surgeons may differ in their treatment of some patient subgroups.

The aim of this study was to determine the extent to which femoral neck fracture patients were treated in agreement with the national guideline. As the guideline states that treatment decision should be based upon patient and fracture characteristics, differences in these characteristics between the treatment groups were also determined.

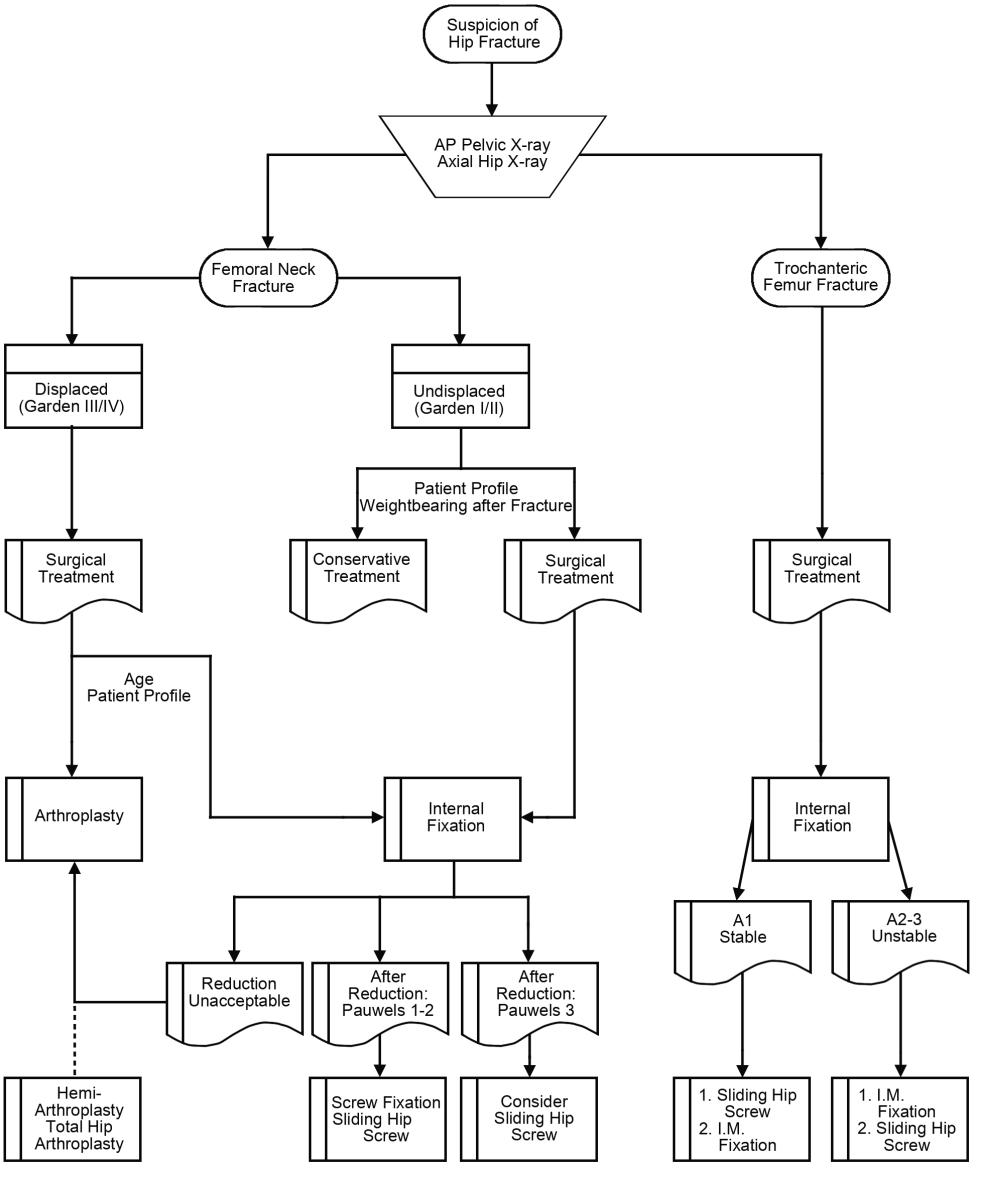

Figure 1. Decision tree for the treatment of hip fracture patients, from the NVvH richtlijn: Behandeling van de proximale femurfractuur bij de oudere mens (Guideline: Treatment of the proximal femoral fracture in the elderly person).[5]

Patients and Methods

Fourteen hospitals participated in this retrospective study. These sites participated in a multicenter randomized controlled trial, the FAITH trial (Fixation using Alternative Implants for the Treatment of Hip fractures, NCT00761813) and formed a femoral neck fracture research network. This network consists of general/trauma surgeons and orthopedic surgeons in four academic hospitals and ten large non-academic hospitals, as both treat femoral neck fractures in the Netherlands.

All consecutive femoral neck fracture patients treated in these hospitals between February 2008 and August 2009 were included. Patients who had been referred to another hospital were excluded. Patients were identified by searching the electronic hospital database for DBC-code (Diagnose Behandel Combinatie; Diagnosis Related Groups (DRG's)), ICD-codes (International Classification of Diseases, version 9/10), and surgical codes. The following data were collected:

- patient characteristics: age, gender, ASA-score, comorbidity (*e.g.*, dementia, arthrosis, malignancies, and cardiac and pulmonary disease), pre-fracture living status, pre-fracture use of aids, and additional injuries;
- fracture characteristics: Garden (*i.e.*, undisplaced versus displaced) and Pauwels (*i.e.*, 1-2 versus 3) classification;
- treatment: type of treatment, surgical delay, surgeon's specialization, quality of reduction and positioning of the implant in internal fixation, and FAITH-participation;

Fracture characteristics were assessed independently by two senior trauma surgeons (MJH and MHJV) from blinded preoperative, peroperative, and postoperative X-rays. They also assessed the quality of reduction and positioning of implants used using criteria as defined in the Dutch NVvH guidelines (Table 1). If two out of three criteria were met, reduction and positioning were scored as 'acceptable'. If the assessment was indecisive, a third trauma surgeon (GRR) independently reviewed the X-rays and reached a final decision.

Table 1. Criteria for acceptable reduction and positioning of the implant for internal fixation of a femoral neck fracture, according to Dutch NVvH guideline.[5]

Acceptable reduction	Varus-valgus dislocation: maximum Garden index: 160–180° [+] Femoral neck shortening neutralized[+] Dorsoventral dislocation: maximum 10° retroversion- 5° anteversion[++]
Acceptable position cancellous screws	One screw placed caudally over the calcar femoris[+] One screw placed over the dorsal cortex[++] Screws positioned into the subchondral bone (maximum distance between screw tip and femoral head lining: 5-10 mm)[+]
Acceptable position sliding hip screw	Screw positioned in the central or caudal 1/3 part of femoral head[+] Screw positioned in the central or dorsal part of femoral head[++] Screw positioned into the subchondral bone (maximum distance between screw tip and femoral head lining: 5-10 mm)[+]

[+] On AP (Anterior-Posterior) view. [++] On axial view.

Statistical Analysis

Analyses were performed using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA).

In order to perform a quantitative analysis of the degree of guideline adherence, we identified the patient subgroups for whom the guideline gives a clear, unambiguous treatment advice (level 1-3). For each patient group with a guideline based treatment proposal (a, b,…, z), the total number of patients in this group were counted (n_a, n_b,…, n_z). Subsequently, the number of patients who actually received the proposed treatment were counted (y_a, y_b,…, y_z). The proportion of provided treatments that corresponded with the guideline recommendations was calculated using the formula: $((y_a + y_b + \ldots + y_{z)} / (n_a + n_b, \ldots + n_z)) \times 100\%$.

Using similar calculations, the proportion of treatments for which adherence was unclear was reported. Guideline adherence was considered unclear if the treatment seemed in contradiction with the guideline, but could have been explained by a patient characteristic that was not collected in this study (*e.g.*, coxarthrosis or a pathological fracture).

Different treatment groups were compared; non-operative versus operative treatment, internal fixation versus arthroplasty, cancellous screws versus sliding hip screw, and hemi-arthroplasty versus total hip arthroplasty.

Continuous variables are presented as medians with interquartile ranges, categorical variables as numbers and percentage. Continuous variables were compared using the Mann-Whitney U-test. Categorical variables were compared using the Chi-squared test. A P-value <0.05 (two-sided) was taken as threshold of statistical significance. A multivariable logistical regression analysis using a forward stepwise approach was performed in order to model the relation between patient and fracture characteristics, and the treatment group. Variables that displayed a P-value <0.1 in univariate analyses and variables which are likely to influence outcome were entered as covariate.

From this study population 194 patients also participated in the FAITH trial. They were randomized between a treatment with sliding hip screw or cancellous screws. Entering 'FAITH participation' as covariate into the regression model had no statistically significant effect on the results. The FAITH patients were therefore not excluded from analyses.

Results

Demographic description of patient, fracture and treatment characteristics

A total of 1355 femoral neck fracture patients were identified. Pre-operative or post-operative X-rays could not be retrieved for 105 patients; these were therefore excluded. The remaining 1250 patients were studied; 22 patients (2%) had been treated with a non-operative treatment, 486 (39%) with internal fixation, and 742 (59%) with arthroplasty. Of the internal fixation patients 290 (60%) had been treated with cancellous screws (CS) and 196 (40%) with a sliding hip screw (SHS). Of the arthroplasty patients 731 (99%) had been treated with a hemi-arthroplasty (HA) and 11 (1%) with a total hip arthroplasty (THA).

Non-operatively treated patients were significantly more often demented, had more often undisplaced fractures, and less often Pauwels 3 fractures, than surgically treated patients. Internal fixation patients were in a better condition than arthroplasty patients; younger, lower ASA-scores, had lower rates of comorbidity, known osteoporosis, medication use, dementia, and pre-fracture aided mobility, and a higher rate of independent living pre-fracture. Internal fixation patients were also less likely to have displaced fractures and Pauwels 3 fractures (Table 2).

Within the internal fixation group the SHS group was significantly older than the CS group, more often demented, and had more often known arthrosis (in other joints). Nevertheless, fewer SHS patients lived independently pre-fracture. In contrast, the CS group had lower ASA-scores, was less likely to have rheumatoid arthritis and osteoporosis, and had displaced fractures more often.

Within the arthroplasty group the THA patients were in a better condition than the HA patients. They were significantly younger, had lower rates of dementia, medication use, or pre-fracture aided mobility. However, they had a higher rate of arthrosis and osteoporosis pre-fracture.

Treatment characteristics were also compared (Table 2). There were differences in the treatment received in academic hospitals (compared with non-academic hospitals) and in the treatment performed by general/trauma surgeons (compared with orthopedic surgeons).

Guideline adherence

Figure 2 shows the patient numbers in the different treatment groups. We identified the patient groups for whom the guideline gives a clear, unambiguous treatment advice.
Undisplaced fractures should be treated either with internal fixation or non-operatively. Of 322 patients with an undisplaced fracture, 247 had been treated with internal fixation, 59 with arthroplasty, and 16 non-operatively.

Patients with a displaced fracture should receive internal fixation if they are 65-80 years, ambulatory and have an ASA-score<3. These characteristics were present in 195 patients, 79 of whom had been treated with internal fixation, and 116 with an arthroplasty. Patients with a displaced fracture aged 65-80, who have an ASA-score>2 should receive an arthroplasty. Of 82 patients with these characteristics, 64 had been treated accordingly, and 18 had been treated with internal fixation. Arthroplasty should also be performed in patients aged >80 years with a displaced fracture. Of 511 patients with these characteristics, 465 were treated with an arthroplasty, 42 with internal fixation and four with a non-operative treatment.

Table 2. Patient, fracture, and treatment characteristics

	Total N=1250	Non-operative* N=22	IF** N=486	Arthroplasty N=742	CS*** N=290	SHS N=196	HA**** N=731	THA N=11
Age[1] (years)	81 (72-87)	81 (70-89)	72 (60-81) [D]	84 (79-88)	75 (62-84) [D]	68 (56-78)	85 (80-88) [D]	62 (51-77)
Gender[2] (female)	804 (64)	18 (82)	264 (54) [D]	522 (70)	159 (55)	105 (54)	517 (71)	5 (46)
ASA-score[2] (ASA>2)	383 (31)	11 (50)	59 (12) [D]	313 (42)	33 (11) [A]	26 (13)	309 (42)	4 (36)
Comorbidity[2]	959 (77)	16 (73)	316 (65) [D]	627 (85)	186 (64)	130 (66)	618 (85)	9 (82)
Pulmonary disease[2]	124 (10)	2 (9)	48 (10)	74 (10)	29 (10) [B]	19 (10)	74 (10)	0 (0)
Cardiac disease[2]	329 (26)	3 (14)	104 (21) [C]	222 (30)	70 (24) [C]	34 (17)	222 (30) [A]	0 (0)
Hypertension[2]	303 (24)	3 (14)	96 (20) [B]	204 (28)	49 (17) [C]	47 (24)	201 (28)	3 (27)
Diabetes[2]	153 (12)	1 (5)	51 (11)	101 (14)	34 (12) [C]	17 (9)	101 (14)	0 (0)
CVA/TIA[2]	176 (14)	3 (14)	52 (11)	121 (16)	30 (10) [B]	22 (11)	121 (17)	0 (0)
Malignancy (past and present)[2]	184 (15)	5 (23)	61 (486) [A]	118 (16)	36 (12) [B]	25 (13)	117 (16)	1 (9)
Dementia[2]	238 (19)	9 (41) [A]	42 (9) [D]	187 (25)	31 (11) [B]	11 (6)	187 (26) [A]	0 (0)
Arthrosis pre-fracture[2]	67 (5)	1 (5)	20 (4)	46 (6)	13 (5) [B]	7 (4)	43 (6) [C]	3 (27)
Rheumatoid arthritis[2]	35 (3)	0 (0)	12 (3)	23 (3)	5 (2) [C]	7 (4)	23 (3)	0 (0)
Osteoporosis pre-fracture[2]	77 (6)	1 (5)	22 (5) [A]	54 (7)	11 (4) [A]	11 (6)	50 (7) [D]	4 (26)
Medication[2]	921 (74)	17 (77)	311 (64) [D]	593 (80)	183 (63)	128 (65)	588 (80) [C]	5 (46)
Additional injuries[2]	61 (5)	1 (5)	29 (6)	31 (4)	18 (6)	11 (6)	31 (4)	0 (0)
Pre-fracture living status[2] (independent)[§§]	700 (56)	12 (55)	362 (75)	326 (44)	204 (70)	158 (81)	320 (44)	6 (55)
No data available	263 (21)	2 (9)	62 (13) [D]	199 (27)	45 (16) [A]	17 (9)	195 (27)	4 (36)
Pre-fracture use of aids[2]	171 (14)	5 (23)	39 (8)	127 (17)	24 (8)	15 (8)	127 (17)	0 (0)
No data available	766 (61)	13 (59)	232 (48) [D]	521 (70)	148 (51)	84 (43)	514 (70) [A]	7 (64)
Garden classification[2] (displaced)	927 (74)	6 (27) [D]	239 (49) [D]	682 (92)	124 (43) [C]	115 (59)	673 (92)	9 (82)
Pauwels classification[2] (Pauwels 3)	492 (39)	3 (14) [A]	171 (35) [D]	318 (43)	94 (32)	77 (39)	312 (43)	6 (55)
Hospital[2] (academic)[§]	154 (12)	6 (27) [A]	71 (15) [A]	77 (10)	31 (11) [C]	40 (20)	73 (10) [C]	4 (36)
Surgical delay[1] (days)	1 (0-1)	N.A.	1 (0-1) [D]	1 (0-1)	1 (0-1)	1 (0-1)	1 (0-1) [A]	2 (1-6)
Surgeon[2] (general or trauma)[§§]	1005 (80)	19 (86) [D]	425 (87) [D]	561 (76)	242 (83) [C]	183 (93)	561 (77) [D]	0 (0)
Surgery performed by[2] (resident)[§§§]	775 (62)	N.A	347 (71) [D]	428 (58)	217 (75)	130 (66)	426 (58) [A]	2 (18)
Reduction[2] (unacceptable)	N.A.	N.A.	37 (8)	N.A.	28 (10) [A]	9 (5)	N.A.	N.A.
Positioning implant[2] (unacceptable)	N.A.	N.A.	45 (9)	N.A.	27 (9)	18 (9)	N.A.	N.A.

IF, Internal Fixation; CS, Cancellous screws; SHS, Sliding Hip Screw; HA, Hemi-Arthroplasty; THA, Total Hip Arthroplasty; CVA, Cerebro Vascular Accident; TIA, Transient Ischemic Attack; N.A., Not applicable

Unavailable data are only presented for variables that had ≥10% unavailable data in any group. Exception: in the THA group data were missing in two patients (18%) for all variables concerning comorbidity.

* P-values are presented for the comparison of non-operative therapy with surgery. ** P-values are presented for the comparison of internal fixation with arthroplasty. *** P-values are presented for the comparison of CS with SHS. **** P-values are presented for the comparison of HA with THA.

[A] P<0.05, [B] P<0.01, [C] P<0.005, [D] P<0.001. Non-significant P-values are not presented. The Mann-Whitney U-test was used for continuous variables, the Chi-squared test for categorical variables.

[1] Data are presented as median with P_{25}-P_{75} given between brackets. [2] Data are presented as number with percentages.

[§] As opposed to non-academic hospital. [§§] As opposed to orthopaedic surgeon. [§§§] As opposed to surgeon. However, >80% of these operations were supervised by a surgeon.

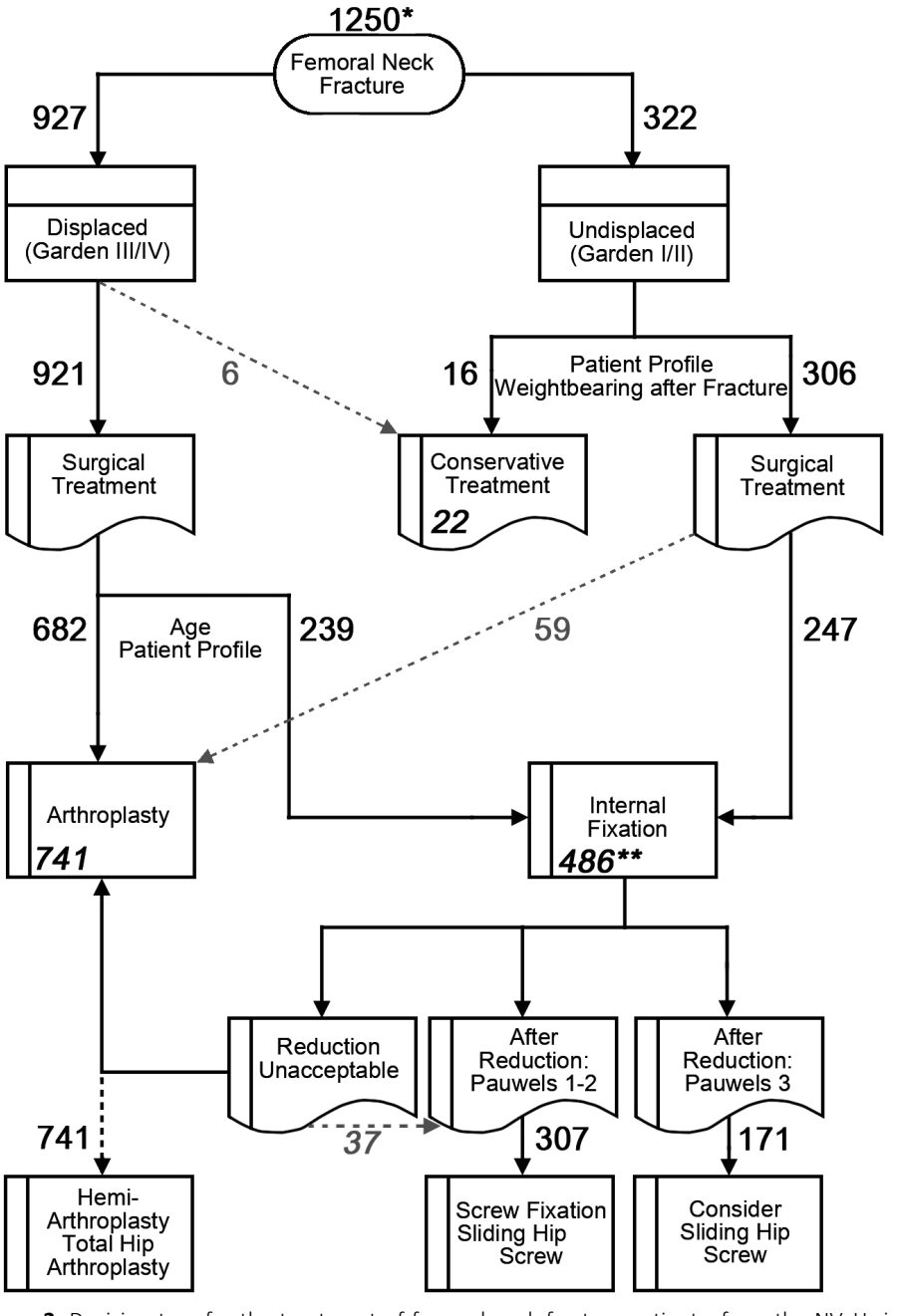

Figure 2. Decision tree for the treatment of femoral neck fracture patients, from the NVvH richtlijn: Behandeling van de proximale femurfractuur bij de oudere mens (Guideline: Treatment of the proximal femoral fracture in the elderly person).[5] Patient numbers are shown.
* Garden classification could not be determined for one patient. **Pauwels classification could not be determined for eight patients. The decision tree could not be completed for these patients.

If internal fixation is chosen for a Pauwels 3 fracture, the guideline recommends using a SHS. Of 171 Pauwels 3 internally fixated fractures, 77 received SHS and 94 CS.

In conclusion, of all treatments that could be quantitatively analyzed for guideline adherence, 74% corresponded with the guideline (Calculation: ((247+16+79+64+465+77)/(322+195+82+511+171))*100%). In 26% the treatment deviated from the guideline. However, in 13% it could not be determined whether the treatment choice could have been explained by a characteristic that was not collected in this study (*e.g.*, coxarthrosis or a pathological fracture). In addition, 37 internal fixation patients with an unacceptable reduction were not converted to arthroplasty, and 45 internal fixation patients had an unacceptable implant position. In total, 72 internal fixation patients did not receive an acceptable treatment (15%).

Differences in characteristics between the treatment groups

Patient and fracture characteristics that independently influenced the treatment decision were studied using multivariable logistic regression models. Compared with internal fixation, patients had a greater chance of receiving an arthroplasty if they were older, had severe comorbidity (ASA-score>2) or osteoporosis diagnosed pre-fracture, a displaced fracture, were mobile pre-fracture using an aid, or if they had been treated by an orthopedic surgeon (odds ratio (OR) 2.2-58.1, Table 3). Patients receiving an arthroplasty were more often aged >80 years and had a higher odds of displaced fractures (OR 51.8 and 58.1, Table 3).

In internal fixation patients, a SHS was preferred over CS in patients with displaced fractures (OR 1.9; 95% CI 1.1-3.1, P=0.021), if they were treated in an academic hospital (OR 2.4; 95% CI 1.0-5.7, P=0.041). CS were preferred by orthopedic surgeons (OR 0.4, 95% CI 0.1-0.9, P=0.037).

Table 3. Odds Ratios for the relation between patient and fracture characteristics, and choice of treatment: internal fixation versus arthroplasty

Determinant		Odds Ratio (95% CI)	P-value
Age group	0-65 years	Reference	
	66-80 years	5.6 (2.5-12.8)	<0.001
	81-100 years	51.8 (18.9-142.2)	<0.001
ASA score	ASA 1-2	Reference	
	ASA 3-4	7.4 (3.0-18.4)	<0.001
Osteoporosis pre-fracture	No	Reference	
	Yes	3.1 (1.0-9.6)	0.045
Pre-fracture mobility	No aids	Reference	
	Using aids	2.2 (1.0-4.7)	0.048
Garden classification	Garden 1-2 (undisplaced)	Reference	
	Garden 3-4 (displaced)	58.1 (20.9-161.2)	<0.001
Surgeon	General or trauma	Reference	
	Orthopaedic	4.2 (1.8-10.1)	0.001

Multivariable logistic regression model, using a forward stepwise approach.
An Odds Ratio>1.0 implies a greater chance of receiving arthroplasty.
Variables not included in the final model were hospital type, gender, arthrosis pre-fracture, rheumatoid arthritis, dementia, medication, pre-fracture living status, and Pauwels classification.

Discussion

Guideline adherence

Overall guideline adherence was considered well, as 74% of the treatments corresponded. Deviations mainly concerned the treatment of elderly patients with a displaced fracture. Although the guideline recommends arthroplasty for patients aged 65-80 years with a displaced fracture and severe comorbidity (*i.e.,* ASA score>2), 22% of these patients were treated with internal fixation. In an international survey 6-26% of the surgeons preferred internal fixation for these patients as well.[6] In addition, 8% of patients aged >80 years with a displaced fracture were treated with internal fixation, whereas the guideline advises arthroplasty. The lack of convincing, irrefutable evidence on the treatment of these patient subgroups is reflected in our results.[6,7,14] A second reason for treatment inconsistency could be the shifting age limit for internal fixation of elderly with displaced fractures in the last decade. Traditionally, an age of 65-75 years was considered a fixed limit for using internal fixation. Now it has progressed to 80 years (in fit, healthy patients). Finally, some surgeons feel that internal fixation should be an acute treatment in all patients. A secondary arthroplasty, if necessary, can then be performed in a planned setting. This strategy may reduce the revision surgery, as the patient's condition can be optimized pre-operatively.

Although the guideline suggests the use of sliding hip screws for Pauwels 3 fractures, 53% of these fractures in our study were treated with cancellous screws. Clearly, there is no agreement on implant selection for the treatment of sheer fractures. Since surgeons were

not interviewed we do not know how many surgeons used the Pauwels classification in their decision making.

Patient and fracture characteristics

Our data showed that characteristics that surgeons consider when deciding on a treatment are age and fracture displacement in particular, but also comorbidity, pre-fracture diagnosed osteoporosis and pre-fracture mobility. These characteristics are compliant with the guideline.[8,17,23] Other characteristics that should be considered are dementia and pre-fracture living status.[8,9,11,23,24] These characteristics did not influence treatment in this study.

Orthopedic surgeons favored arthroplasty more often than general/trauma surgeons did. Orthopedic surgeons may have more affinity with arthroplasty, as they perform arthroplasties more often (*e.g.*, for arthrosis). Moreover, in the Netherlands total hip arthroplasties are performed by orthopedic surgeons only. Although it is comprehensible to perform a treatment that one is comfortable with, patient outcome should come first. Likewise, the treatment should not differ between academic and non-academic hospitals.

The strength of this study is the inclusion of a large, representative population. Participating surgeons represent both orthopedic and trauma/general surgeons in academic and non-academic hospitals in five different trauma regions nationwide. The guideline that was studied, is based on the best available international evidence at the time of development, and is therefore applicable internationally. Our results may stimulate others to perform similar research, as there are no guideline adherence studies concerning hip fracture treatment available at this moment, to the best of our knowledge.

Obviously, this study has limitations. The retrospective nature made it difficult to collect data on some characteristics that probably affected treatment decision (*e.g.*, pathological fracture, osteoarthrosis, or rheumatoid arthritis). However, as these characteristics are considered absolute contraindications for internal fixation, we expect that all surgeons provided the indicated treatment in these specific patients. A second limitation is the Pauwels classification assessment. It is known that the inter-observer agreement of the Pauwels classification on pre-operative X-rays is low.[25] All X-rays were assessed in duplicate in order to obtain the highest reliability possible. Finally, there was unfortunately no option to question the surgeons about their motivation to deviate from the guideline.

In summary, overall adherence to the guideline for femoral neck fracture treatment was good, as 74% of the treatments corresponded. Most deviations concerned the treatment of elderly (age 65-80 years and >80 years) with a displaced fracture, and the implant choice in internal fixation. Additional data, preferably with a higher scientific level of evidence is needed in order to improve the guideline and to reinforce a more uniform treatment of these patients.[10]

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Chapter 5

Cumulative incidence and treatment of non-simultaneous bilateral femoral neck fractures in a cohort of one thousand two hundred and fifty patients

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Abstract

Purpose: In the Netherlands, over 20,000 patients sustain a hip fracture yearly. A first hip fracture is a risk factor for a second, contralateral fracture. Data on the similarity of the treatment of bilateral femoral neck fractures is only scarcely available. The objectives of this study were to determine the cumulative incidence of non-simultaneous bilateral femoral neck fractures and to describe the patient characteristics and treatment characteristics of these patients.

Methods: A database of 1,250 consecutive patients with a femoral neck fracture was available. Patients with a previous contralateral femoral neck fractures were identified by reviewing radiographs and patient files. Patient characteristics, previous fractures, hip fracture type and details on treatment were collected from the patient files.

Results: One hundred nine patients (9%, 95% confidence interval 7–10%) had sustained a non-simultaneous bilateral femoral neck fracture. The median age at the first fracture was 81 years; the median interval between the fractures was 25 months. Overall, 73% was treated similarly for both fractures in terms of non-operative treatment, internal fixation or arthroplasty. In patients with identical Garden classification (30%), treatment similarity was 88%.

Conclusions: The cumulative incidence of non-simultaneous bilateral femoral neck fractures was 9%. Most patients with identical fracture types were treated similarly. The relatively high risk of sustaining a second femoral neck fracture supports the importance of secondary prevention, especially in patients with a prior wrist or vertebral fracture.

Introduction

Hip fractures are a global public health problem. In the Netherlands, over 20,000 patients sustain a hip fracture annually.[1] The incidence of hip fractures is expected to increase, mainly due to the aging of the population. A first hip fracture is a risk factor for sustaining a second hip fracture at the contralateral side. Other reported predictors for a second hip fracture include age, female gender, living alone, alcoholism, any prior fracture, functional status, dementia and osteoporosis.[2–6]

Despite a declining trend in hip fractures in Western countries, a worldwide increase is expected as a result of aging of populations by improving health care globally and increasing industrialisation and urbanization.[7-12] An increase in the incidence of the first hip fracture implies that an increase in the incidence of a subsequent hip fracture is to be expected as well. The latter is associated with an increased mortality risk; the 1-year mortality ranges from 9 to 27% following a first hip fracture and from8 to 32% after a second hip fracture.[2,13,14] The five year mortality rate after a first and second hip fracture is 46 and 67%, respectively.[2]

The overall cumulative incidence of non-simultaneous bilateral hip fractures, regardless of fracture location or subtypes, is reported to range from 2 to 15%.[2–4,6,15–22] The reported interval between both fractures is two to five years.[2–4,6,13,15,18,21,22] In 60–81% of the patients with bilateral hip fractures, the second fracture is of the same type as the first hip fracture (*i.e.,* trochanteric or femoral neck).[3,4,13,14,18,21,23] Most reports on characteristics of bilateral hip fractures involved patients with both trochanteric and femoral neck fractures. A minority of patients with a primary trochanteric fracture sustains a subsequent contralateral femoral neck fracture. The opposite, a femoral neck fracture as a second fracture with a first trochanteric fracture, is even rarer.[14,17] Especially the treatment of non-simultaneous femoral neck fractures has received little attention in previous studies.

Controversy on the treatment of active patients with a displaced femoral neck fracture still exists, particularly on the type of implant [*i.e.,* sliding hip screw (SHS) or cannulated hip screws (CHS)] or prosthesis (*i.e.,* hemi-arthroplasty or total hip arthroplasty). One would expect that two fractures of the same type in patients with unchanged characteristics would be treated the same. In addition to these patient and fracture characteristics, preferences of the surgeon may also contribute to the treatment selection. Detailed information on the treatment of patients with non-synchronous femoral neck fractures is limited, to the best of our knowledge.

Therefore, the objectives of this study were to determine the cumulative incidence of non-simultaneous bilateral femoral neck fractures and to describe patient characteristics, mortality and treatment characteristics of these patients.

Patients and Methods

This study was conducted as a multicentre retrospective cohort study of patients who sustained non-simultaneous bilateral femoral neck fractures. The study was approved by the local Medical Research Ethics Committee (ref. no. MEC- 2011-419, approval date 4 November 2011). In a previous retrospective multicentre study, a database was developed, containing data for 1,250 consecutive patients with a femoral neck fracture who were treated in 14 Dutch hospitals between February 2008 and August 2009.[24] Patients were identified by searching the electronic hospital databases for Diagnosis Treatment Combination code (DBC; comparable to the North American Diagnosis Related Groups), surgical codes and International Classification of Diseases codes (ICD, versions 9 and 10).

Two investigators (PTPWB and AKEM) independently assessed pelvic and hip X-rays of all patients for the presence of any sign of a previous fracture at the contralateral side (*i.e.,* implant, arthroplasty or healed fracture). Presence of a non-simultaneous bilateral femoral neck fracture was confirmed with data in the patient files.

Patients were eligible for enrolment if details on the treatment (*i.e.,* non-operative treatment, type of implant or arthroplasty) of both femoral neck fractures were available from radiographs or medical correspondence. Pathological fractures, simultaneous bilateral fractures and fractures following a high energetic trauma were excluded.

The following data were collected for both fractures:

– Patient characteristics: age at fracture, gender, American Society of Anesthesiologists (ASA) class, prior and concomitant fractures

– Fracture characteristics: Garden classification (*i.e.,* undisplaced or displaced)

– Treatment characteristics: type of treatment, and for internal fixation, quality of reduction and positioning of the implant (*i.e.,* acceptable or unacceptable)

– Post-treatment details: length of hospital stay and in-hospital mortality

The Garden classification was assessed independently by two senior trauma surgeons (MJH and MHJV) from blinded pre-operative, peri-operative and postoperative X-rays; classifications were done according to the description made in 1961.[25] These surgeons also rated the quality of reduction and positioning of the implant (for internal fixation), using the criteria as defined in the guideline of the Association of Surgeons of the Netherlands, as described elsewhere (Table 1).[24,26] If two of three criteria were met, fracture reduction and positioning of implants were scored as ‘acceptable’. Disagreement was solved by a third senior trauma surgeon (GRR), who independently reviewed the X-rays in order to reach a final decision.

Table 1. Criteria for acceptable reduction and positioning of the implant for internal fixation of a femoral neck fracture, according to Dutch NVvH guideline.[16]

Acceptable reduction	Varus-valgus dislocation: maximum Garden index: 160–180° [+] Femoral neck shortening neutralized[+] Dorsoventral dislocation: maximum 10° retroversion- 5° anteversion[++]
Acceptable position cancellous screws	One screw placed caudally over the calcar femoris[+] One screw placed over the dorsal cortex[++] Screws positioned into the subchondral bone (maximum distance between screw tip and femoral head lining: 5-10 mm)[+]
Acceptable position sliding hip screw	Screw positioned in the central or caudal 1/3 part of femoral head[+] Screw positioned in the central or dorsal part of femoral head[++] Screw positioned into the subchondral bone (maximum distance between screw tip and femoral head lining: 5-10 mm)[+]

[+] On AP (Anterior-Posterior) view. [++] On axial view.

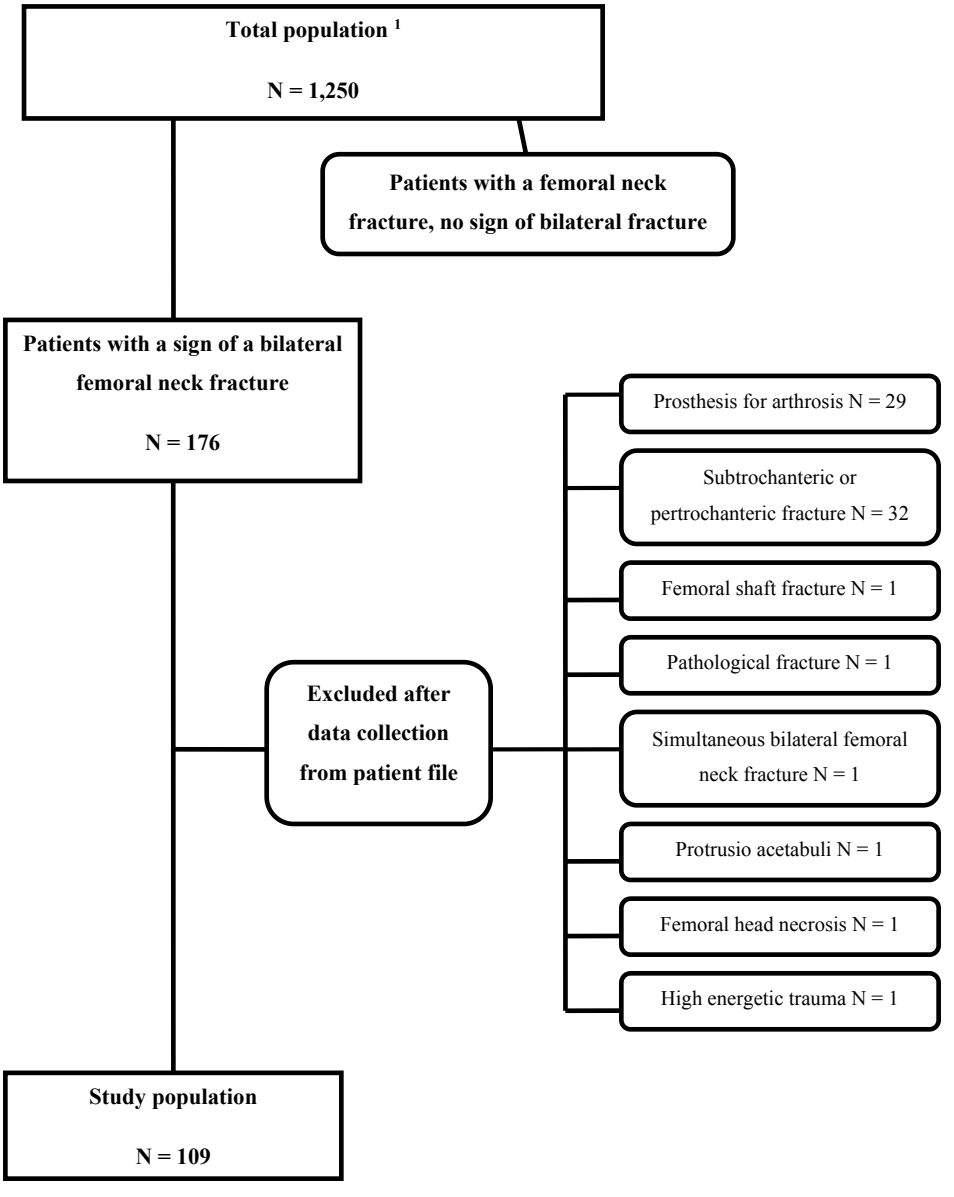
Statistical analysis

Statistical analyses were conducted using SPSS (SPSS Inc. released 2007, SPSS for Windows, Version 16.0, SPSS Inc., Chicago, IL, USA). Normality of continuous data was tested with the Shapiro-Wilk test and by inspecting frequency histograms (Q-Q plots). All continuous variables were nonparametric and are therefore presented as medians with the first and third quartiles. Categorical variables are presented as numbers with percentages. The traditional Wald confidence interval (CI) formula for proportions was used for calculating the 95% CI around the cumulative incidence of bilateral femoral neck fractures. Descriptive analyses were performed in order to describe the patient, treatment and postoperative variables for the first and second fractures. An additional analysis of treatment was performed for a subgroup of patients in whom the Garden class of the first and second fractures were of the same type.

Results

Patient demographics

The total population consisted of 1,250 patients with a femoral neck fracture. Of these, 176 patients showed radiographic signs of bilateral femoral neck fractures. After reviewing the medical files, 67 patients were excluded; 29 patients underwent arthroplasty because of arthrosis rather than a fracture, 32 patients had a subtrochanteric or pertrochanteric fracture and six patients were treated for a reason other than for osteoporotic femoral neck fracture (Figure 1). In the remaining 109 patients, the occurrence of non-simultaneous bilateral femoral neck fractures (9%, 95% CI 7–10%) was confirmed.



[1] Patient population with a femoral neck fracture between February 2008 and August 2009 treated in 14 Dutch hospitals

Figure 1. Flowchart of enrolled patients

Patient characteristics of these 109 included patients are shown in Table 2. The median age was 81 years (P25–P75 74–86 years) at the time of the first fracture and 86 years (P25–P75 79–89 years) at the time of the second fracture. Seventy-six patients (70%) were female. The median time between the first and the second fracture was 25 months (P25–P75 12–62 months). The shortest interval between the two fractures was three days (and occurred following a fall) and the longest was 20 years. The right hip was the first affected side in 51 patients (47%). At the time of the first fracture 30 of 41 patients (73%) for whom data were available lived at home. At the time of the second fracture 49 of 80 patients (61%) lived at home. Concomitant fractures were found in 5% of patients at the time of the first fracture and in 7% of patients at the time of the second fracture. Twenty-two patients (20%) had sustained another type of fracture prior to the second femoral neck fracture, with a median interval of seven years. Especially fractures of the wrist (6%), humerus (7%), spine (1%), rib (2%), olecranon (2%) and foot (2%) were found. The median hospital length of stay was ten days (P25–P75 seven to 17 days) after the first fracture and 9 days (P25–P75 five to 13 days) after the second. One patient (1%) died during admission for treatment of the second fracture. Of the 1,141 excluded patients, 42 (3.7%) died in hospital.

Table 2. Patient characteristics by first and second fracture

Characteristic	Overall N=109	First Fracture N=109	Second fracture N=109
Age [1] (years)		81 (74-86)	86 (79-89)
Female gender [2]	76 (70)		
Right side affected [2]		51 (47)	58 (53)
Additional injuries at presentation [2]		5 (5)	8 (7)
Wrist/hand fracture		4 (4)	1 (1)
Humeral fracture		0 (0)	3 (3)
Tibia fracture		0 (0)	1 (1)
Head injury/wound		1 (1)	3 (3)
Not documented		34 (31)	3 (3)
Prior other fracture [2]	23 (21)		
Not documented	27 (25)		
Pre-operative ASA-class [2]			
ASA I-II		21 (19)	65 (57)
ASA III-IV		12 (11)	34 (31)
Unknown		76 (70)	13 (12)

[1] Data are displayed as median, with the first and third quartile in parentheses;
[2] Patient numbers are displayed, with the percentages in parentheses;

Fracture and treatment characteristics of the first and second femoral neck fracture
Details of the fractures and treatments of the total population of 109 patients are shown in Table 3. Data on the Garden classification of the first fracture were available in 50% of the patients. In patients for whom data were available, the first fracture was displaced in 72% of the patients (39 of 44); the second fracture (with 90% data availability) was displaced in 68% (67 of 98). Arthroplasty was performed in 65% of the first fractures and in 70% of the second fractures. The majority was treated with a hemi-arthroplasty (92 and 99% of the first and second fractures, respectively). Internal fixation was applied in 35 patients for the first fracture (32%) and in 30 patients (28%) for the second fracture. In these patients, CHS were then used in 49% of the first fractures and 70% of the second fractures. A SHS was used in 49 and 30% of the first and second fractures, respectively.

An overview of similarity in characteristics and treatment of the first and second fractures is shown in Table 4. Data are presented for the entire group of 109 patients as well as for a subgroup of 33 patients in whom both fractures had the same Garden classification. This subgroup was treated identically in 88% of the patients in terms of non-operative treatment, internal fixation or arthroplasty. When the type of implant and arthroplasty were also taken into account, bilateral fractures of the same Garden classification were treated similarly in 73%. If arthroplasty was used, the same type of device was used in 100% of patients, whereas only in two of seven patients (27%) treated with internal fixation was the same type of implant used. Table 5 shows the relation between Garden classification and treatment for the total population of 109 patients. Undisplaced fractures were mostly treated with internal fixation, 67% of the first fractures and 58% of the second fractures. Displaced fractures were treated with arthroplasty in 82% of first and in 81% of second fractures.

Table 3. Fracture and treatment characteristics by first and second fracture

Characteristic	First fracture N=109	Second fracture N=109
Garden classification		
Non-displaced (Garden I-II)	15 (14)	31 (28)
Displaced (Garden III-IV)	39 (36)	67 (62)
Missing[1]	55 (51)	11 (10)
Therapy		
Non-operative treatment	3 (3)	3 (3)
Internal Fixation	35 (32)	30 (28)
CHS	17 (16)	21 (19)
SHS	17 (16)	9 (8)
PFNA	1 (1)	0 (0)
Arthroplasty	71 (65)	76 (70)
Hemi-arthroplasty	65 (60)	75 (69)
Total hip arthroplasty	6 (6)	1 (1)
Internal fixation: Reduction		
Adequate	20 (57)	28 (93)
Not adequate	0 (0)	2 (7)
Not able to determine	4 (11)	0 (0)
Missing	11 (31)	0 (0)
Internal fixation: Implant position		
Adequate	19 (54)	26 (87)
Not adequate	1 (3)	4 (13)
Not able to determine	4 (11)	0 (0)
Missing	11 (31)	0 (0)
Implant position CHS		
Adequate	8 (47)	17 (81)
Not adequate	1 (6)	4 (19)
Not able to determine	2 (12)	0 (0)
Missing	6 (35)	0 (0)
Implant position SHS		
Adequate	11 (65)	9 (100)
Not adequate	0 (0)	0 (0)
Not able to determine	1 (6)	0 (0)
Missing	5 (29)	0 (0)

PFNA; Proximal femoral nail antirotation, CHS; Cannulated hip screws, SHS; sliding hip screw.
Patient numbers are displayed with percentages in parentheses.
[1] Garden classification could not be determined if adequate diagnostic images were not available, *e.g.,* if trauma diagnostics had been done at another hospital.

Table 4. Identical characteristics and treatment of first and second fracture

	Entire group (N=109)	Same Garden classification for both fractures (N=33)
ASA classification	15/109 (14)	10/33 (30)
Garden class	33/109 (30)	N.A.
Treatment[1]	62/109 (57)	24/33 (73)
Treatment[2]	80/109 (73)	29/33 (88)
Type of prosthesis[3]	54/60 (90)	22/22 (100)
Type of implant[3]	8/20 (40)	2/7 (29)
Reduction[3]	11/20 (55)	5/7 (71)
Position implant[3]	9/20 (45)	6/7 (86)
Position CHS[3]	2/4 (50)	2/2 (100)
Position SHS[3]	2/4 (50)	N.A.

N.A; not applicable, CHS; Cannulated hip screws, SHS; sliding hip screw.
Data are shown as numbers with the percentage in parentheses.
[1] Treatment separated into non-operative, CHS, SHS, PFNA, hemi-arthroplasty and total hip arthroplasty.
[2] Treatment separated into non-operative, internal fixation, and arthroplasty.
[3] Data are shown for the subgroup of patients (denominator) where this applies and for whom data were available for both fractures.

Table 5. Association between the Garden classification and treatment (all 109 patients)

Treatment	Garden I-II	Garden III-IV	Unknown
First fracture	N=15	N=39	N=55
Non-operative	2	0	1
Internal fixation	10	7	18
Arthroplasty	3	32	39
Second fracture	N=31	N=67	N=11
Non-operative	1	1	1
Internal fixation	18	12	0
Arthroplasty	12	54	10

Data are shown as numbers.

Discussion

Of 1,250 patients with a femoral neck fracture, 109 had previously sustained a contralateral femoral neck fracture. The cumulative incidence of non-simultaneous bilateral fractures was 9%. This result is comparable with the recent literature, reporting a cumulative incidence of bilateral proximal femur fractures between 2 and 20% depending on the follow-up period.[2–6,13,15,17] These studies however included both trochanteric and femoral neck fractures, implying that the cumulative incidence of bilateral femoral neck fractures in these studies had been lower than the percentages reported.

The median time between the first and second fracture in our study was 25 months (P25–P75 12.4–61.8 months). This is in line with literature data, where intervals from two to five years between the first and second hip fracture are reported.[2,4,6] Given this short period, substantial changes in patient characteristics were not very likely.

Additional injuries, especially fractures, are likely to impair postoperative rehabilitation, to prolong hospital stay and to increase the total health care costs. In this study, concomitant additional significant injuries such as a wrist fracture, head injury or humeral fracture were seen in 5 and 7% of the patients at the time of the first and second hip fracture, respectively. Approximately a quarter of patients had already had a fracture in their medical history, prior to femoral neck fracture (28%), which corresponds with a previous study on non-simultaneous bilateral femoral neck fractures (30%).[16] These results emphasize the vulnerability of this population, as a prior fracture increases the risk of a hip fracture and the occurrence of a first hip fracture increases the risk of subsequent (hip) fracture.[5,23] In the growing, fragile population that often suffers from multiple risk factors for falling and sustaining subsequent fractures, there might be great potential for multidisciplinary secondary prevention strategies. In this retrospective study, documentation of osteoporosis screening was found in only 19% of the patients and anti-osteoporosis medication was prescribed in only 24% (data not shown). This indicates too little attention has been paid to osteoporosis screening and management. Although circumstances and protocols differ between hospitals, there is a clear need for better compliance with the Dutch guideline on osteoporosis and fracture prevention.[27] Regular evaluation of the local progress of the implementation should ensure a stricter protocol compliance and ultimately a better quality of fracture care.[28] Also, independent community-dwelling elderly have an increased risk of sustaining a second hip fracture.[2] This emphasizes that the environment of the patient (*i.e.,* modifications in their home) and adequate rehabilitation (i.e. appropriate use of walking aids and physical therapy) deserve attention to minimize the risk of falling and sustaining a new fracture as much as possible.

Over 80% of the displaced fractures were treated with arthroplasty and about 60% of the undisplaced fractures were treated with internal fixation. It seems that trauma and orthopaedic surgeons generally agree on the treatment of the different types of femoral neck fractures, as 88% of the patients with a bilateral femoral neck fracture with similar Garden classification were treated similarly in terms of a non-operative treatment, internal fixation or arthroplasty.

However, heterogeneity in the use of the specific type of implant or prosthesis remains. This is supported by the finding that in only 27% of the patients with an identical Garden classification of both fractures the type of treatment was not the same when the type of implant/arthroplasty was also considered. Heterogeneity was especially high in the use of implant for internal fixation. This was not unexpected, as insufficient evidence on the use of

implant or arthroplasty type for femoral neck fractures is known.[29] It was however unexpected that the controversy in the essential details of treatment seemed larger in undisplaced fractures (67 versus 58% internal fixation in first and second fracture), than in displaced fractures (82 versus 81% arthroplasty in first and second fracture). Diverging treatment decisions may however partially be explained by other variables such as coxarthrosis, co-morbidity, surgeons' preferences and material availability.

The strength of our study is that a database of a large number of 1,250 consecutive patients treated in 14 different hospitals was used.[24] However, due to the retrospective design, data were incomplete from a substantial number of patients. Data concerning the first fracture were often missing for patients in whom the first fracture was treated at another hospital. In addition, some radiographs were not available, e.g. when they were made analogously, during external storage or during digital exportation. There are no indications for a selective pattern of missingness of data. As a consequence, a reliable multivariable analysis was not possible.

For the same reason, the one year mortality could not be calculated; therefore, the in-hospital mortality was used as a relevant alternative. Moreover, as no data on the cumulative incidence in a matched control cohort were available, it was not possible to carry out a risk assessment. Due to the relatively small number of patients per hospital, a subgroup analysis of similarity of management for both fractures if treated at the same hospital was not possible. It is unfortunate that data on osteoporosis or osteoporosis treatment were often not documented. As discussed above, attention to osteoporosis screening and treatment can still be improved. For this reason, osteoporosis guidelines were implemented in 1999 and revised in 2002 and 2011.[28] Despite duplicate assessment of radiographic images, non-operatively treated fractures or fractures in which implants had been removed could have been missed. However, if only the slightest doubt existed patient files were checked; in none of those patients was a previous fracture confirmed. Therefore, it is unlikely that bilateral fractures were missed.

Conclusion

In a population of 1,250 patients who sustained a femoral neck fracture during the study period, 9% had previously sustained a femoral neck fracture at the contralateral side. The median time interval between both fractures was 25 months. If both fractures were undisplaced or both were displaced, the same treatment was applied in 88% of patients. Surgeons generally agreed on the use of internal fixation or arthroplasty for the different types of femoral neck fractures. The relatively high risk of sustaining a second femoral neck fracture supports the importance of national secondary prevention guidelines, especially in patients with a prior wrist or vertebral fracture.

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Chapter 6

The societal costs of femoral neck fracture patients treated with internal fixation

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Abstract

Summary: The study rationale was to provide a detailed overview of the costs for femoral neck fracture treatment with internal fixation in the Netherlands. Mean total costs per patient at 2-years follow-up were €19,425. Costs were higher for older, less healthy patients. Results are comparable to internationally published costs.

Purpose: The aim of this study was to provide a detailed overview of the cost and healthcare consumption of patients treated for a hip fracture with internal fixation. A secondary aim was to compare costs of patients who underwent a revision surgery with patients who did not.

Methods: The study was performed alongside the Dutch sample of an international randomized controlled trial**,** concerning femoral neck fracture patients treated with internal fixation. Patient characteristics and healthcare consumption were collected. Total follow-up was two years. A societal perspective was adopted. Costs included hospital costs during primary stay and follow-up, and costs related to rehabilitation and changes in living situation. Costs were compared between non-revision surgery patients, implant removal patients, and revision arthroplasty patients.

Results: A total of 248 patients were included (mean age 71 years). Mean total costs per patient at two years follow-up were €19,425. In the non-revision surgery patients total costs were €17,405 (N=137), in the implant removal patients €10,066 (N=38), and in the revision arthroplasty patients €26,733 (N=67). The main contributing costs were related to the primary surgery, admission days, physical therapy, and revision surgeries.

Conclusions: The main determinant was the costs of admission to a rehabilitation center/ nursing home. Costs were specifically high in elderly with comorbidity, who were less independent pre-fracture, and have a longer admission to the hospital and/or a nursing home. Costs were also higher in revision surgery patients. The two years follow-up costs in our study were comparable to published costs in other Western societies.

Introduction

The worldwide incidence of hip fractures is increasing from an estimated 1.26 million patients per year in 1990, 1.6 million in 2000, to an estimated 4.5-6.3 million by 2050.[1-3] Accordingly, the incidence of hip fractures in the Netherlands increased from 7,614 per year in 1981 to 21,000 per year in 2010.[4,5] Globally, the annual estimated worldwide direct and indirect costs of hip fractures amounted to $34.8 billion in 1990, and are expected to rise to an estimated $131 billion by 2050.[2]

Detailed information on healthcare costs are gaining importance as the burden of health care costs threatens to exceed the financial resources available. It is therefore necessary to focus on options to cut down health care expenses. Costs of hip fracture treatment should receive attention, as hip fractures account for over two third of all hospital admission days due to fractures, the incidence is increasing worldwide, and hip fracture treatment leads to substantial costs. In the Netherlands, the total costs of hip fractures amounted to €13.600 per patient in 1999.[6] This was a crude estimate of costs based on national databases and registrations, concerning costs of hip fracture patients, treated with various implants and prostheses. A number of studies compared the costs of treatment with internal fixation with costs of treatment with arthroplasty.[7-13] These studies demonstrated either similar or higher costs for patients treated with internal fixation, ranging from €13,000 to €57,197 per patient after a two-year follow-up period (Table 1). Comparison between the studies is impeded however by the differences in follow-up period and in the costs that were studied. In some studies costs were confined to in-hospital health care costs, whereas other studies also included costs caused by rehabilitation or changes in living situation. The studies are often based on limited patient numbers. It is therefore likely that the presented costs are not all a correct estimation of the actual costs involved. To the best of our knowledge, detailed analysis of the costs of internal fixation for hip fractures in the Netherlands has never been performed. In the Netherlands, hip fracture care pathways are implemented in an increasing number of hospitals, promoting early mobilization, early hospital discharge, and rehabilitation in a specialized nursing home department or at home. These pathways are designed to optimize patient care and health care cost.

The aim of this study was to provide a detailed overview of the costs of patients with a femoral neck fracture treated with internal fixation. A societal perspective was adopted, including costs of health care and costs incurred outside health care. This information can be used for economic evaluations. A secondary aim was to compare costs of patients who underwent a revision surgery with patients who did not, to study the burden of extra costs caused by revision surgeries.

Table 1. Studies describing the costs of treatment of femoral neck fracture patients with internal fixation

Author	Country	N	Follow-up	Average costs per patient
Iorio *et al.* (2001)	US	123	2 yrs	€27,474[a]
Haentjens *et al.* (2003)	Belgium	14	1 yr	€15,255 [a]
Rogmark *et al.* (2003)	Sweden	36	2 yrs	€18,564 [a]
Johansson *et al.* (2006)	Sweden	78	2 yrs	€13,100
Alolabi *et al.* (2009)	Canada	61	1 yr	€12,977 [a]
Frihagen *et al.* (2010)	Norway	112	2 yrs	€47,186
Waaler Bjørnelv *et al.* (2012)	Norway	86	2 yrs	€57,197

[a] US Dollars were converted to Euros using year-specific exchange rates (www.statistics.dnb.nl)

Patients and Methods

This cost study was a cohort study performed alongside the Dutch sample of the FAITH trial (Fixation using Alternative Implants for the Treatment of Hip fractures, NCT00761813), an international randomized controlled trial concerning femoral neck fracture patients treated with internal fixation. The study was approved by the local medical research ethics committee.

Population

In the Netherlands 14 hospitals participated and enrolled 250 consecutive patients in the period between February 2008 and August 2009. Patients were eligible if they (1) were adults aged ≥50 years, (2) had a radiologically confirmed femoral neck fracture (*i.e.*, either undisplaced fracture, or displaced fracture in ASA 1-2 patients (American Society of Anesthesiologists classification) aged 50-80 years with a fracture that could be reduced closed), (3) had a low energy fracture without other major trauma, and (4) were ambulatory pre-fracture (with or without aid). Patients were excluded if they (1) had a fracture not suitable for internal fixation (*e.g*,. pathological fracture, rheumatoid arthritis, or osteoarthritis), (2) had associated major injuries of the lower extremities, (3) had retained hardware around the hip, (4) had an infection around the hip, (5) had a bone metabolism disorder other than osteoporosis, (6) were moderately or severely cognitively impaired pre-fracture, (7) had dementia or Parkinson's disease severe enough to compromise the rehabilitation process, or (8) were not likely to be able to complete follow-up.

Treatment and follow-up

All patients had medical optimization before surgery. Patients with undisplaced fractures were treated within seven days of presentation, patients with displaced fractures within two days. Patients were treated with internal fixation (*i.e.*, either two or three cancellous screws or a sliding hip screw). Early mobilization was encouraged, with weight bearing as tolerated. Post-operative osteoporosis screening and treatment was recommended in all patients.

Follow-up measurements were performed at 2 weeks, 10 weeks, 6 months, 9 months, 12 months, 18 months, and 24 months after the primary surgery.

Cost measurement

The study adopted a societal perspective including the following costs: (1) hospital costs during the primary stay, (2) hospital costs during follow-up including cost of hip-related adverse events and revision surgeries, and (3) non-hospital costs of rehabilitation and aids. (Table 2). Data on resource use were collected prospectively at the scheduled follow-up contacts and at the close-out visits at the end of the study. Use of hospital resources was collected in the study case report forms (items are listed in Supplemental Table 1), and from the patient's hospital file. The latter had 100% capture. These data were supplemented with data from a patient self-administered questionnaire, a customized version of the 'Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness' (Tic-P), which has been validated for use in healthcare cost studies.[14,15] An English version of the original Tic-P is available online.[16] The questionnaire included questions on stay in a rehabilitation center or nursing facility, number of contacts with the medical specialist and physical therapist, medication and the use of aids (*e.g.*, walker, crutches, and wheelchair). The total number of consumption units per cost category per patient was multiplied by the unit prices. The unit prices (anno 2010) for all cost categories are presented in Table 2. The costs for use of the operating room, including cost for personnel, anesthesia, and overhead costs, as well as implant and general equipment costs were calculated based on data derived from one of the participating academic hospitals and three regional hospitals, and one surgical equipment and implant firm. Means were calculated and considered a realistic estimation of the average prices in the participating sites.

For most other healthcare resources reference cost prices were derived from the Dutch manual on cost research, methods and standard costs in economic healthcare evaluations.[17] Costs from 2008 and 2009 were adjusted to 2010 terms using the national consumer price index. Unit prices for radiologic and other diagnostic procedures were taken from the NZa (Nederlandse Zorgautoriteit; Dutch Healthcare Authority) which are assumed to provide a good indication of the actual costs. Medication costs were calculated using standard medication prices as described by the CVZ (College voor zorgverzekeringen; Health Care Insurance Board), online available on www.medicijnkosten.nl (Supplemental Table 2). The costs for the use of several aids (*i.e.*, crutches, walker, or extra facilities at home) were obtained from at a home care firm that is representative of the Dutch market. These costs were used as an estimation of the actual costs for the use of aids in all participating patients, as these costs are fairly standard and will not vary to a large extent across the country. Costs of aids were calculated according to the annuity method, applying an interest rate of 4.5% and a 10-year write off period.

Table 2. Sources and unit costs (2010) of healthcare resources

Cost categories	Unit	Source of consumption data	Source of valuation	Unit price (€)
Hospital costs – primary stay				
Emergency department visit	Visit	Hospital registry	Cost manual[1]	152.92
Radiology/Diagnostic studies				
X-ray	X-ray	Hospital registry	NZa[2]	51.63
CT-scan pelvis	CT-scan	Hospital registry	NZa[2]	227.22
MRI scan pelvis	MRI scan	Hospital registry	NZa[2]	261.47
Ultrasound	Ultrasound	Hospital registry	NZa[2]	82.09
DEXA scan	DEXA scan	Hospital registry	NZa[2]	109.22
Skeletal scintigraphy	Scintigraphy	Hospital registry	NZa[2]	185.37
Surgery				
Surgeon	Hour	Study registry (Case report Form)	Cost manual[1]	137.22[a] / 104.31[b]
Operating room*	Hour	Study registry (Case report Form)	Hospital/industry data[3]	560.94[a] / 704.51[b]
Additional costs after hours	Hour	Study registry (Case report Form)	Hospital/industry data[3]	75.36[a]/ 94.65[b]
Equipment and implant				
Cancellous screws	Operation	Study registry (Case report Form)	Hospital/industry data[3]	490.30
Sliding Hip Screw	Operation	Study registry (Case report Form)	Hospital/industry data[3]	504.91
Admission days	Day	Study registry (Case report Form)	Cost manual[1]	440.53[a] / 582.31[b]
Hospital costs – follow-up				
Radiology/Diagnostic studies				As described above
Out-patient clinic visits	Visit	Hospital registry + patient questionnaire[§]	Cost manual[1]	130.64[a] / 64.81[b]
Adverse events				
Medication**	Dose per day	Hospital registry + patient questionnaire[§]	CVZ[4]	N.A.
Emergency department visit	Visit	Hospital registry	Cost manual[1]	152.92
Admission days	Day	Study registry (Case report Form)	Cost manual[1]	440.53[a] / 582.31[b]
Revision surgery				
Surgeon	Hour	Study registry (Case report Form)	Cost manual[1]	137.22[a] / 104.31[b]
Operating room*	Hour	Study registry (Case report Form)	Hospital/industry data[3]	560.94[a] / 704.51[b]
Equipment and implant				
Hemiarthroplasty	Operations	Study registry	Hospital/industry data[3]	1685.64
Total Hip Arthroplasty	Operations	Study registry	Hospital/industry data[3]	1722.39
Gammanail	Operations	Study registry	Hospital/industry data[3]	1241.51
Extended gammanail	Operations	Study registry	Hospital/industry data[3]	1258.39
Implant removal	Operations	Study registry	Hospital/industry data[3]	53.16
Soft tissue debridement	Operations	Study registry	Hospital/industry data[3]	25.29
Antibiotic beads	Operations	Study registry	Hospital/industry data[3]	567.79
Antibiotic spacer	Operations	Study registry	Hospital/industry data[3]	496.26
Admission days	Day	Study registry (Case report Form)	Cost manual[1]	440.53[a] / 582.31[b]
Medication***	Dose per day	Hospital registry + patient questionnaire[§]	CVZ[4]	N.A.

Costs related to rehabilitation / changes in living situation				
Rehabilitation center/Nursing home				
Elderly home	Days	Patient questionnaire§	Cost manual[1]	91.14
Nursing home	Days	Patient questionnaire§	Cost manual[1]	241.03
Rehabilitation clinic	Days	Patient questionnaire§	Cost manual[1]	344.32
Home nursing day	Hours	Patient questionnaire§	Cost manual[1]	35.44
Physical therapy (outpatient)				
Physical therapy	Session	Patient questionnaire§	Cost manual[1]	36.46
Mensendieck / Cesar therapy	Session	Patient questionnaire§	Cost manual[1]	35.45
Use of aids				
Crutches	Day	Patient questionnaire§	Home care firm[5]	0.07
Walker	Day	Patient questionnaire§	Home care firm[5]	0.08-0.14
Wheelchair	Day	Patient questionnaire§	Home care firm[5]	0.25
Electric scooter	Day	Patient questionnaire§	Home care firm[5]	0.66
Extra bed	Day	Patient questionnaire§	Home care firm[5]	1.15
Extra toilet facilities	Day	Patient questionnaire§	Home care firm[5]	0.09-0.19
Extra shower facilities	Day	Patient questionnaire§	Home care firm[5]	0.09-0.17

N.A.; Not applicable

Reference unit costs anno 2010 were used, or costs were adjusted to 2010 costs using the national consumer price index.

*Including operating room personnel, anesthesia, and overhead costs. **Mainly antibiotics. ***Hip fracture related medication only (*i.e.,* pain medication and osteoporosis medication; see Supplemental Table 2 for details).

§ Patient questionnaire; Customized version of the 'Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness'.

[1] Cost manual; Manual on cost research, methods and standard costs in economic healthcare evaluations, version 2010[17], [2] NZa; Nederlandse Zorgautoriteit (Dutch Healthcare Authority) standard costs. [3] Hospital/industry data; costs were requested from one academic hospital, three regional hospitals, and one surgical equipment and implant firm. Means were calculated and used as an estimation of the real costs in all participating sites. [4] CVZ; Standard prices were used as described by the CVZ (College voor zorgverzekeringen; Health Care Insurance Board), online available on www.medicijnkosten.nl. [5] Home care firm; costs of aids were requested from a home care firm and costs per day were calculated based on the calculated daily annuity. These costs were used as an estimation of the real costs in all participating patients.

[a] Academic hospital, [b] General hospital.

Over 90% of the study population consisted of retired elderly. Consequently, the indirect costs due to productivity losses were considered less relevant for this population and a minor contribution to the overall costs in this study, and were excluded. Costs of home care were also excluded from the analyses. Most elderly patients that received home care were not capable of estimating the amount of hours that they received home care. Moreover, it was impossible to discriminate home care due to the hip fracture from home care for other medical reasons. Reliable cost calculations were therefore impossible. Costs of osteoporosis screening and treatment were included, but not presented as a separate group: costs of a DEXA scan were included in radiology/diagnostic studies costs, costs of visits to an osteoporosis specialist were included in outpatient clinic visits costs, and costs for osteoporosis treatment were included in medication costs.

Statistical analysis

Analyses were performed using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA). Missing values for cost items were replaced using multiple imputation following the predictive mean matching method, using ten imputations. Means and standard deviations (SD) were calculated. Costs were calculated in the total population and in three subgroups (1) patients who did not require a revision surgery, (2) patients who had their implant removed (without any other revision surgery), and (3) patients who underwent one or multiple revision surgeries. Group 2 consisted of patients with a successfully healed fracture. Patients who had other, less common, revision surgeries (*i.e.,* replacement of implant by other implant, shorter screw, or revision to gamma nail) were not included in these subgroup-analyses. Costs between the subgroups were compared with a one-way ANOVA. Post-hoc comparisons using independent samples student T-tests were performed.

Results

Demographic description of patients

Of the 649 consecutive femoral neck fracture patients treated in the study period, 294 patients were eligible following the inclusion and exclusion criteria for this study, of which 250 were randomized (Figure 1). Two patients could not be followed; one patient turned out not to have a femoral neck fracture and one patient withdrew consent immediately after randomization.

The study group had a mean age of 71 years (SD 10) and 60% was female. Patients were relatively healthy and independent pre-fracture. Prior to the fracture only 3% of the patients were institutionalized and 13% used an aid for mobilization. Thirteen percent had severe comorbidities (*i.e.*, ASA>2). The most common comorbidities were hypertension (42%), cardiac disease (21%), or pulmonary disease (16%). Forty-six percent of the fractures was displaced (*i.e.*, Garden III-IV) and 35% was a Pauwels 3 fracture.

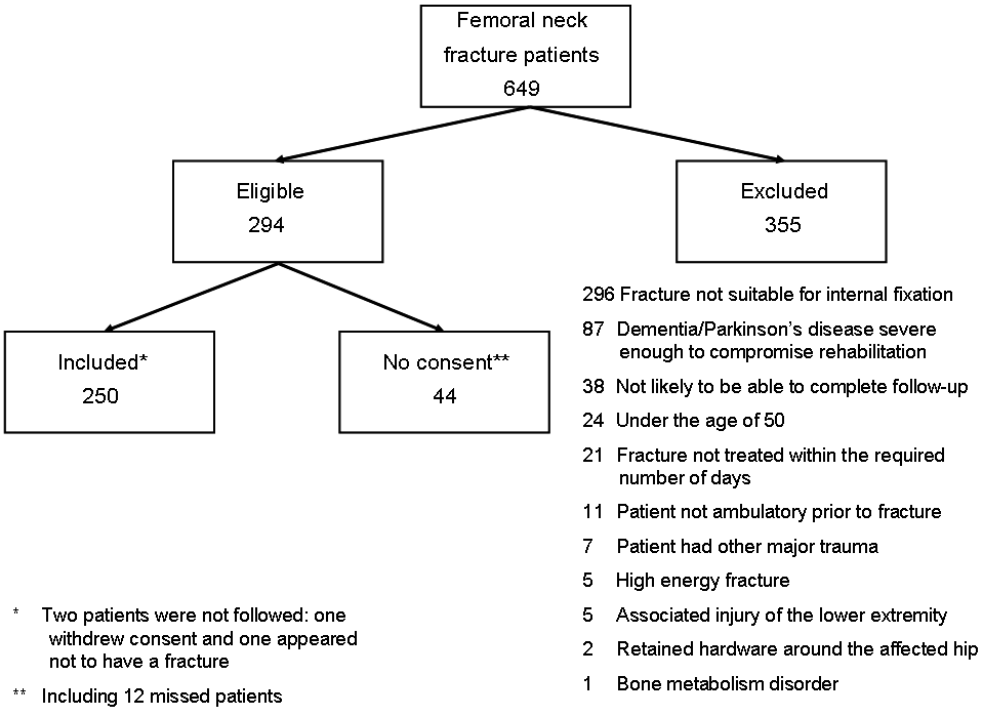

Figure 1. Flowchart of patients participating in the study

Treatment and clinical outcome

Patients were admitted to the hospital during 7 days on average. After discharge, 22% percent of the patients rehabilitated in a nursing home, whereas 72% of the patients were able to go home. An adverse event occurred in 101 patients (41%), of whom 12 patients had an implant- or surgery-related adverse event, and 13 patients sustained a wound infection. Other adverse events were a urinary tract infection, delirium, or various non-hip related adverse events, which were all infrequent (*i.e.,* less than 10 patients each). In 38 patients (15%) the implant was removed after the fracture had healed because of persisting implant-related complaints. A revision to an arthroplasty occurred in 67 patients (27%), of which 45 patients received a total hip arthroplasty. Out of 67 patients that had a revision to arthroplasty, the revision had been performed in 52 patients by one year follow-up, in 36 patients by six months follow-up, and in 23 patients by ten weeks follow-up. The main reason for the revision surgery was the occurrence of avascular necrosis and/or non-union. The mean follow-up was 25.5 months (SD 6.1).

Costs

An overview of the costs is shown in Table 3. Most costs were generated in the first treatment year. The total mean costs per patient at 10 weeks follow-up amounted to €9,781 (SD € 6,909). The costs in this primary treatment phase were mainly related to the primary surgery (mean €1,313; SD € 497), the hospital admission days (mean €4,322; SD €3,104), and the admission days in a rehabilitation center or skilled nursing facility after hospital discharge (mean €2,735; SD €5,226).

Table 3. Mean costs of femoral neck fracture patients treated with internal fixation (N=248)

Cost categories	Cost until 10 weeks (€)	Costs until 1 year (€)	Costs until 2 years (€)
Hospital costs – primary stay			
Emergency department visit	152 (152-152)	152 (152-152)	152 (152-152)
Radiology/Diagnostic modalities	243 (207-361)	243 (207-361)	243 (207-361)
Surgery	1,313 (793-2,506)	1,313 (793-2,506)	1,313 (793-2,506)
Admission days	4,322 (1,762-9,287)	4,322 (1,762-9,287)	4,322 (1,762-9,287)
Total	6,031 (3,392-11,090)	6,031 (3,392-11,090)	6,031 (3,392-11,090)
Hospital costs – follow-up			
Radiology/Diagnostic modalities	212 (103-472)	441 (127-981)	544 (207-1,163)
Out-patient clinic visits	134 (65-261)	370 (165-792)	452 (194-1,023)
Adverse events	39 (0-45)	54 (0-111)	128 (0-697)
Revision surgery	154 (0-1500)	512 (0-2,117)	707 (0-2,287)
Medication	30 (0-112)	88 (0-324)	157 (0-555)
Total	568 (168-1,989)	1,465 (378-4171)	1,988 (480-4,838)
Costs related to rehabilitation / changes in living situation			
Rehabilitation center/Nursing home	2,735 (0-15,076)	7,452 (0-39,991)	9,425 (0-46,308)
Physical therapy (outpatient)	418 (0-1006)	1,354 (231-3,169)	1,850 (292-4,752)
Use of aids	28 (5-104)	76 (5-245)	131 (5-466)
Total	3,181 (27-15,782)	8,883 (487-41,743)	11,406 (540-51,300)
Total costs	9,781 (3,993-24,203)	16,379 (4,977-52,339)	19,425 (5,237-58,874)

Costs are presented as cumulative mean costs at each follow-up moment with 95% confidence interval between brackets.

At one year follow-up, the total mean costs per patient were €16,379 (SD €17,319), €6,598 more than at 10 weeks follow-up. The total mean costs per patient in the second year of follow-up amounted €3,046. The total mean costs per patient after two years were on average €19,425 (SD €24,200). The main contributing cost categories in the first and second year of follow-up were similar: (1) the costs related to the admission days in a rehabilitation center or skilled nursing facility (*i.e.*, €7,452 per patient in the first year and €1,973 in the second year), (2) the costs related to physical therapy at home or in an outpatient physical therapy clinic (*i.e.*, €1,354 per patient in the first year and €496 in the second year), and (3) the costs of revision surgery and related hospital admission days (*i.e.*, €512 per patient in the first year and €195 in the second year). In 5 patients, there were extremely high costs for the

primary hospital admission (*i.e.,* more than €10,000), mainly due to a prolonged length of stay. In three patients this was caused by multiple adverse events and revision surgeries, and an admission to the ICU. In two patients, no reason could be found for the prolonged length of stay. Radiologic studies and other diagnostic studies (*i.e.*, €544; SD 343) and out-patient clinic visits (*i.e.*, €452; SD 267) contributed more than one percent to the total treatment costs of the patients at two years follow-up (Figure 2).

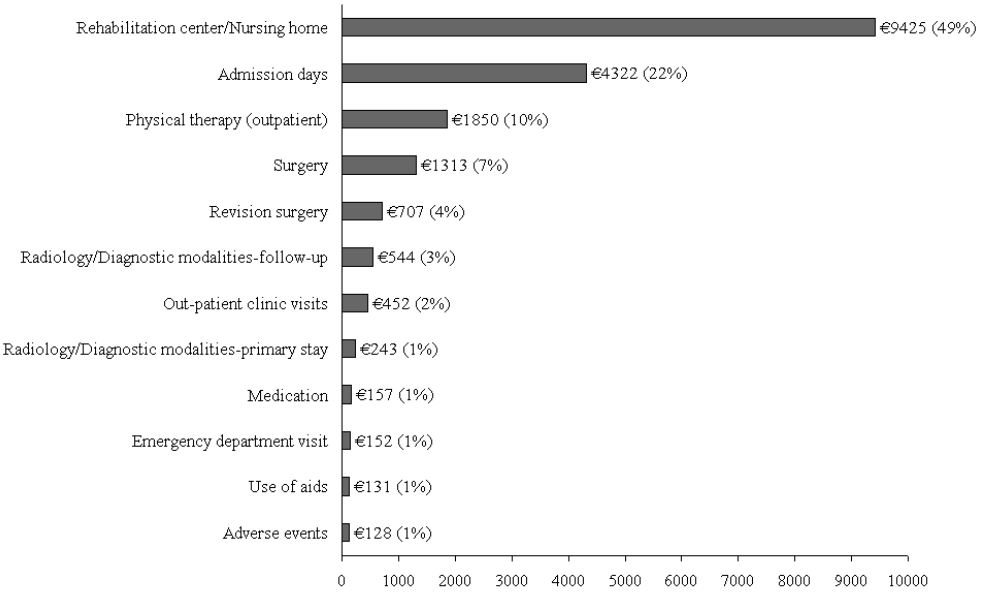

Figure 2. Relative contribution of various cost categories to the total treatment costs of patients until two years follow-up.

At two years follow-up, the costs were highest for patients who underwent a revision to arthroplasty (total mean costs per patient €26,733; SD €24,151) (Table 4). Costs per patient were lowest for patients who did not require revision surgery; €17,405 (SD €25,842). Patients who had had their implant removed had lower costs (total mean costs per patient €10,066; SD €5,484; P 0.001). These differences were seen throughout all follow-up moments.

Table 4. Costs of patients without revision surgery, patients who had an implant removal, and patients who required revision surgery

	No revision surgery (N=137)	Implant removed* (N=38)	Revision surgery to arthroplasty (N=67)	P-value
Costs until 10 wks	9,371 (3,970-24,339)	6,967 (3,394-19,322)	11,549 (5,125-29,762)	0.003
Costs until 1 year	14,438 (4,824-45,211)	8,723 (4,434-19,735)	22,498 (8,052-73,307)	<0.001
Costs until 2 years	17,405 (4,953-58,865)	10,066 (4,843-26,731)	26,733 (9,465-80,029)	0.001

Costs are presented as cumulative mean costs at each follow-up moment with standard deviations between brackets.
Differences between the three groups were compared with a one-way ANOVA. Post-hoc comparisons using independent samples student T-tests were performed and indicated that all subgroups had significant differences in costs at all follow-up moments (*i.e.,* P<0.005).
Six patients were excluded from the subgroup analyses as these patients all had other, less common, revision surgeries (*i.e.,* replacement of implant by other implant, shorter screw, or revision to gamma nail)
* This group consisted of patients that healed successfully.

Discussion

The total mean costs per femoral neck fracture patient treated with internal fixation were €16,379 at one year follow-up and €19,425 at two years follow-up. This is slightly higher than the €13,600 estimated in 1999 from national database records, including similar cost categories (cost corrected for inflation €17,478, using http://statline.cbs.nl).[6] One should realize that the costs presented include crude costs only, excluding hospital overhead costs and taxes, as is usual for economic analyses. This should be taken into account when calculating budgets.

The cost estimates in our study are comparable with previous studies from Western societies, although other studies usually did not incorporate all cost categories that were included in the present study. This may indicate that the hip fracture care pathways as implemented in the Netherlands promoting early mobilization, early hospital discharge, and rehabilitation in a specialized nursing home department or at home lead to limited costs. The costs in our study are even >50% lower than published costs in 2010 and 2012 for Norway (Table 1).[7-13] Differences can be explained by several factors. The Norwegian studies involved older patients, all suffering from displaced fractures, and who were more often institutionalized pre-fracture, and less mobile without an aid pre-fracture, with more severe comorbidity (including the cognitively impaired). All patients were treated in a university hospital, which induces higher costs in general. Additionally, the unit costs per admission day to the hospital and to a nursing home were higher in Norway. The revision surgery rate in our study was comparable with previously published rates and will therefore not have influenced differences in costs between our study and previously published cost data.[8,13,18-20]

The main determinant in the total costs was the costs for admission to a rehabilitation facility or nursing home. However, these costs may represent an overestimation of the actual cost related to the hip fracture. It is difficult to determine if the hip fracture was the only reason for temporary or permanent stay in a nursing home. Especially in elderly patients this is usually multifactorially influenced by general condition, other comorbidities or fractures, and the availability of informal care. Another important determinant was the costs for the primary hospital admission, similar as reported in other studies. In our study, the length of stay was shorter than in some other studies.[8,11,12] This distribution of costs in the Netherlands seems an effect of the hip fracture care pathways described above. Other determinants that substantially contributed to the total costs were the costs for primary surgery (7%) and the costs for physical therapy in the out-patient clinic (10%). Reducing the amount of physical therapy should not be a focus to reduce costs, as intensive physical therapy has proven to benefit patient outcomes and independency.[21] Most costs were generated in the first year. In the second year only 16% of the costs were generated. A two years follow-up was considered sufficient, as it is known that most interventions, treatments and rehabilitation of the targeted patient population will take place in that period.[19] A subset of patients, however, will become permanent nursing home residents after their hip fracture, thereby extending their societal costs beyond the two years time span. This may not only be caused by the hip fracture, as discussed above.

As expected, costs were highest for patients who underwent a revision to arthroplasty. After two years, the costs per patient were on average €9,328 per patient higher than for the patients that did not require revision surgery. This amount is in agreement with previous data, and is attributed to additional costs for surgery, hospital admission, and rehabilitation.[8] Baseline characteristics of the patients that underwent a revision to arthroplasty (*i.e.,* age, comorbidity, and pre-fracture living status and mobility) were similar as for patients that did not. Costs were lowest for patients who had their implant removed after fracture healing. This may seem unexpected, as the implant removal is associated with costs for the surgical intervention. Patient selection is the most likely explanation for the relatively low costs. The implant removal patients were younger, healthier, more independent and mobile pre-fracture. They therefore probably required less care and rehabilitation, generating less costs. Their superior pre-fracture mobility and hence perhaps higher rehabilitation goals may also be an indication for their implant removal. Within the patient group that did not have a revision surgery, no potential factors were correlated with higher costs other than the previously mentioned patient characteristics (*i.e.,* age, ASA score and mobility pre-fracture).

Our study has some limitations. As the population was relatively young, healthy, and independent pre-fracture, the presented costs may not be representative for all hip fracture patients. Moreover, not all cost categories related to hip fracture care were included. Costs of home care, informal care, and transport could not be reliably reproduced by patients. These

costs are however expected not to contribute significantly to the total costs, compared with the costs that were included. Societal costs due to productivity losses were also excluded, but these are not expected to contribute significantly as well as these patients are older and mainly retired. Taking these limitations into account, the presented costs are probably an underestimation of the actual costs involved, especially for the patients that rehabilitated at home. However, the current study is one of few studies analyzing costs of hip fracture treatment with internal fixation in detail, including both hospital costs and costs of the rehabilitation process. Another strength of our study is the sample size, being the highest of all studies published until now.

In conclusion, the total mean costs per femoral neck fracture patient treated with internal fixation were €16,379 at one year follow-up and €19,425 at two years follow-up. These costs are comparable with costs published from previous studies in Western societies. The hip fracture care pathways implemented in the Netherlands promoting early mobilization, early hospital discharge, and rehabilitation in a specialized nursing home department or at home, seem successful and contributory to limiting health care costs. Highest costs are generated by patients who underwent a revision to arthroplasty. This reinforces the importance of attempting to reduce the potentially avoidable risk of a revision surgery by a careful selection of patients for internal fixation, not only for medical reasons, but also economical reasons.

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Supplemental Table 1. Hospital resource items included in the case report forms

1.	Date of visit to emergency room
2.	Duration of primary admission (calculated from date of admission and date of discharge)
3.	Duration of primary surgery (calculated from start time and end time of surgery)
4.	Primary surgery during the day or during after-hours
5.	Type of implant used during primary surgery
6.	Location of primary surgery (*i.e.*, academic or non-academic hospital)
7.	Number and date of follow-up visits to the out-patient clinic
8.	Number and type of diagnostic modalities (*i.e.*, X-rays, CT/MRI scans, ultrasound, bone scintigraphy, dexa scans)
If applicable:	
9.	Duration of secondary admission for revision surgery or adverse event (calculated from date of admission and date of discharge)
10.	Duration of revision surgery (calculated from start time and end time of surgery)
11.	Revision surgery during the day or during after-hours
12.	Type of revision surgery (*e.g.*, implant removal, revision to (hemi)arthroplasty)
13.	Location of revision surgery (*i.e.*, academic or non-academic hospital)
14.	Type of adverse event and type of treatment for this event (*e.g.*, medication, injection)

Supplemental Table 2. Medication prices

Medication name	ATC code	Price per tablet (€)
Acetylsalicylzuur/Ascal (80 mg)	N02BA01	0.03
Actokit	M05BB	1.22
Alendroninezuur/Fosamax (70 mg)	M05BA04	0.10
Arthrotec (50 mg)	M01AB55	0.25
Calcium/Calci-Chew (2.5 g)	A12AA04	0.43
Calcium + Colecalciferol (2.5 g/800 IE)	A12AX	0.30
Celebrex (200 mg)	M01AH01	0.80
Ciprofloxacine (500 mg)	J01MA02	0.12
Clindamycine (150 mg)	J01FF01	0.33
Dalteparine/Fragmin (injection, 0.2 ml)	B01AB04	3.51
Depo-medrol + Lidocaine (injection, 5 ml)	H02BX01	11.43
Colecalciferol/Devaron (800 IE)	A11CC05	0.15
Diclofenac/Voltaren (50 mg)	M01AB05	0.27
Etoricoxib/Arcoxia (30 mg)	M01AH05	0.63
Flucloxacilline (500 mg)	J01CF05	0.10
Fosavance (70 mg/5600 IE)	M05BB03	3.73
Glucosamine (1178 mg)	M01AX05	0.60
Indometacine (50 mg)	M01AB01	0.06
Marcaine (injection, 5 ml)	N01BB01	0.46
Nadroparine/Fraxiparine (injection, 0.3 ml)	B01AB06	1.75
Risedroninezuur/Actonel (35 mg)	M05BA07	0.16
Tramadol (50 mg)	N02AX02	0.02

ATC code; Anatomical Therapeutic Chemical Classification System.
Medication costs were calculated using standard medication prices as described by the CVZ (College voor Zorgverzekeringen; Dutch National Health Care Insurance Board), online available on www.medicijnkosten.nl. In this overview, the price for the most commonly used dose is presented. The cheapest available price was used in the calculations.
The total medication price was calculated by multiplying the price per tablet by the number of tablets used per day and the number of days that the medication was used. Delivery costs (€6.35 per three months) were added to these costs.

Part III

Chapter 7

Femoral neck shortening after internal fixation of a femoral neck fracture

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Abstract

This study assesses femoral neck shortening and its effect on gait pattern and muscle strength in patients with femoral neck fractures treated with internal fixation. Seventy-six patients from a multicenter randomized controlled trial participated. Patient characteristics and Short Form 12 (SF-12) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were collected. Femoral neck shortening, gait parameters, and maximum isometric forces of the hip muscles were measured and differences between the fractured and contralateral leg were calculated. Variables of patients with little or no shortening, moderate shortening, and severe shortening were compared using univariate and multivariate analyses. Median femoral neck shortening was 1.1 cm. Subtle changes in gait pattern, reduced gait velocity, and reduced abductor muscle strength were observed. Age, weight, and Pauwels classification were risk factors for femoral neck shortening. Femoral neck shortening decreased gait velocity and seemed to impair gait symmetry and physical functioning. In conclusion, internal fixation of femoral neck fractures results in permanent physical limitations. The relatively young and healthy patients in our study seem capable of compensating. Attention should be paid to femoral neck shortening and proper correction with a heel lift, as inadequate correction may cause physical complaints and influence outcome.

Introduction

The worldwide incidence of hip fractures is increasing, from an estimated 1.6 million persons per year in 1990 to 6.3 million by 2050. The disability adjusted life-years lost as a result of hip fractures ranks in the top 10 of all cause disability globally.[1-3] Femoral neck fractures can be treated with internal fixation. A sliding hip screw or multiple cancellous screws are implants of choice.[4] Research on the treatment of femoral neck fractures with internal fixation is traditionally aimed at fracture healing, revision surgery, morbidity, and mortality.[5, 6] In addition, self-reported functional outcome is often measured using health related quality of life questionnaires (*e.g.,* Short-Form 12 (SF-12), EuroQol 5D (EQ-5D)), or disease specific questionnaires (*e.g.,* Harris Hip Score (HHS), Western Ontario McMaster Osteoarthritis (WOMAC).[5, 7, 8]

However, little is known about the physical limitations that may result from internal fixation following femoral neck fractures. Surgery, immobilization after surgery, and pain may cause an abnormal or asymmetrical gait pattern and reduced muscle strength. It is unknown to what extent internal fixation patients show adequate recovery. Asymmetries in gait pattern and muscle strength have never been measured and can be plausible explanations for a reduced mobility and quality of life. Gait analysis may even add information to the results from functional questionnaires such as the WOMAC.[9] Its value has been proven in clinical studies after other surgical interventions, such as hip arthroplasty.[10]

Femoral neck shortening is another potentially important limitation that may arise and affect gait pattern and muscle strength. Implants allow fracture fragments to slide along the implant and permit impaction at the fracture site, especially when subjected early to an axial loading force during weight bearing. The biomechanical rationale behind these implants is that compression of fracture fragments will stimulate fracture consolidation. However, this may also lead to femoral neck shortening and leg length discrepancy, changing the abductor muscles moment arm, causing screw back out, and affecting standing posture or gait.[11-16]

The current authors hypothesized that femoral neck shortening would occur in femoral neck fracture patients treated with internal fixation, leading to long-term functional impairment with reduced muscle strength and an asymmetrical gait pattern. The goal of this study was to determine the level of femoral neck shortening and asymmetry in gait and muscle strength in patients who sustained femoral neck fractures treated with internal fixation at least one year before. Risk factors for femoral neck shortening and the effect of femoral neck shortening on physical functioning were determined.

Patients and Methods

Population

This study (clinical trial registration number, NL32419.078.10) was a secondary cohort study to the Dutch sample of an international randomized controlled trial, the FAITH trial (Fixation using Alternative Implants for the Treatment of Hip fractures, NCT00761813). The primary objective of the FAITH trial was to assess the impact of sliding hip screw versus cancellous screw fixation on rates of revision surgery at two years in elderly patients with femoral neck fractures. In the Netherlands 14 hospitals participated and enrolled 250 patients (February 2008-August 2009). Patients were recruited for the Dutch FAITH trial if they (1) were adults aged ≥50 years, (2) had a radiologically confirmed femoral neck fracture (*i.e.*, undisplaced fracture or displaced fracture in ASA 1-2 patients (American Society of Anesthesiologists classification), aged 50-80 years, with a fracture that could be closed reduced) (3) had a low energetic fracture without other major trauma, and (4) were ambulatory pre-fracture (with or without aid). Patients were excluded if they (1) had a fracture not suitable for internal fixation (*e.g.*, pathological fracture, rheumatoid arthritis, or osteoarthritis), (2) had associated major injuries of the lower extremities, (3) had retained hardware around the hip, (4) had an infection around the hip, (5) had a bone metabolism disorder other than osteoporosis, (6) were moderately or severely cognitively impaired pre-fracture, (7) had dementia or Parkinson's disease severe enough to compromise the rehabilitation process, or (8) were not likely to be able to complete follow-up. All patients had an acceptable fracture reduction according to their surgeon, and were allowed weight bearing as tolerated after initial surgery. Patients were included in the current study at least one year after internal fixation, because it is generally believed that only little functional improvement can be expected after one year. Exclusion criteria for this study were:

- Revision surgery or conversion to arthroplasty
- Patient not capable of walking several meters independently (with or without ambulatory aid)
- Other lower limb abnormalities that could be expected to influence gait pattern (*e.g.,* other lower extremity fractures/neurological diseases)
- History of previous internal fixation or arthroplasty of the contralateral (control) hip
- X-rays inadequate for measuring femoral neck shortening.

The study was approved by all local Medical Research Ethics Committees.

Measurements

Measurements and data collection were performed during a single visit to the outpatient clinic. Femoral neck shortening was measured on digital X-rays using graphic software (Photoshop CS3 Graphic, Adobe, San Jose, USA) as described previously.[12, 13] The most recent

anterior-posterior X-ray of the fractured hip was compared with the contralateral hip on X-rays taken at the time of the injury. The uninjured side was outlined, overlapped over the fractured side and adjusted for differences in size. Femoral neck shortening was measured in the vertical plane. Known diameters of screws were used in order to correct for differences in magnification of the X-rays.

Gait analysis was measured using a calibrated pressure plate (footscan®, RSscan International, Olen, Belgium; 2.0 x 0.4m, 125 Hz). Patients were instructed to walk barefoot across the plate at their preferred speed. All patients completed this task without an aid. Five measurements were performed per patient. The combination of at least three gait measurements that were most representative were selected based upon the coefficient of variation, and used for analysis. The following temporospatial gait parameters were analyzed: step length, duration of stance phase, single and double support phase, foot axis, progression of the center of pressure line (COP), and gait velocity. Data of the fractured leg were compared with the contralateral side (as usual in gait studies). The difference was computed using the formula: $\text{Parameter}_{\text{fractured leg}} - \text{Parameter}_{\text{contralateral leg}}$.

To analyze the plantar pressure, data were normalized for foot size, width, and progression angle as described by Keijsers et al.[17] This is a validated method, which allows for a more detailed and standardized comparison of the fractured side with the contralateral side (intraclass correlation ≥ 0.85). Figures were computed that show the difference in pressure distribution between the legs by subtracting pressure in the contralateral leg from the pressure in the fractured leg, for each activated sensor. A t-test was used to detect significant differences in plantar pressure distribution.

Maximum isometric forces of the hip muscles were measured using a handheld dynamometer (MicroFET®, Biometrics BV, Almere, the Netherlands). Flexion, extension, abduction and adduction strength were measured in a supine position. The means of triplicate measurements were calculated, and the differences between the affected extremity and control side were computed.

Baseline characteristics, surgical data, rehabilitation data, and WOMAC and SF-12 scores were available from the FAITH trial.[18, 19] SF-12 scores were converted to a norm-based score and compared with the norms for the general population of the United States (1998), as weighing factors for the Dutch population were not available. Patients' satisfaction with their gait pattern was measured using a VAS (Visual Analog Scale) score, ranging from zero (extremely dissatisfied) to ten (completely satisfied). A VAS was also used to measure to which extent patients were hampered due to the leg length difference, ranging from zero (free of complaints) to ten (very hampered).

Data analysis

Analyses were performed using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA). Patient and fracture characteristics, femoral neck shortening, gait parameters, muscle strength, and quality of life scores were determined for the study sample. Continuous variables are presented as medians with interquartile ranges, categorical variables as numbers and percentage. In order to study femoral neck shortening the study population was divided in tertiles: patients with little or no femoral neck shortening (<0.75 cm), moderate shortening (0.75-1.50 cm) and severe shortening (>1.50 cm). Groups were compared using a Kruskal-Wallis Analysis of Variance (ANOVA; numeric variables) or a Chi-squared analysis (categorical variables). In order to assess if femoral neck shortening independently influences gait velocity and patient functioning (WOMAC score), a multivariable regression analysis was performed, using a backward stepwise approach. Variables that displayed a P-value <0.1 in the univariate analyses and variables which were likely to influence the outcome variable were entered as covariate. Results with P<0.05 (two-sided test) were regarded as statistically significant.

Results

Demographic description of patients

Of the initial group of 250 patients, 114 patients had to be excluded following the in- and exclusion criteria. Of the remaining 136 patients 76 participated (Figure 1). The burden of an additional hospital visit was the main reason for refused participation. Characteristics of the non-participating patients (*i.e.*, age, ASA score and pre-fracture use of aids) did not differ significantly from those in the included population.

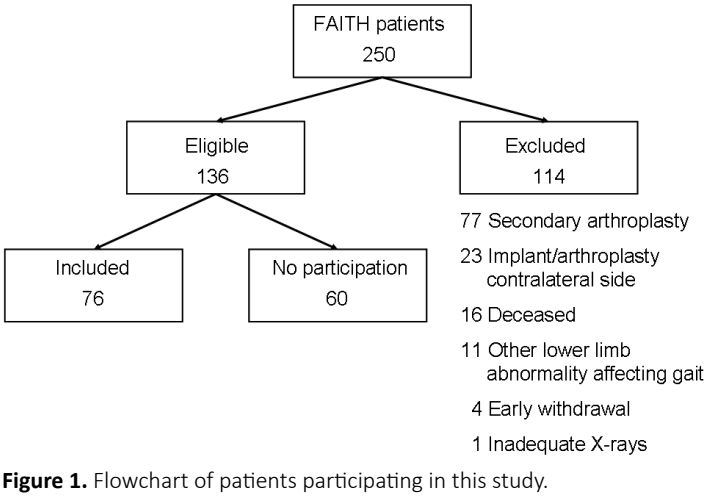

Figure 1. Flowchart of patients participating in this study.

The study population consisted of relatively young and healthy femoral neck fracture patients, with a median age of 68.3 years. Only 7% had severe comorbidities (ASA score>2). Prior to the fracture only 1% of the patients were institutionalized and 8% used an aid for mobilization. Approximately 35% of all fractures were displaced, 29% had a Pauwels 3 fracture. Femoral neck shortening measurements were performed at median 11.7 months after the initial surgery. Gait and strength measurements were performed at median 22.4 months after the initial surgery (Table 1). At that time, all fractures had healed.

Table 1. Patient and fracture characteristics

	Total (N=76)	**Little or none FNS (<0.75 cm) (N=25)**	**Moderate FNS (0.75-1.50 cm) (N=26)**	**Severe FNS (>1.50 cm) (N=25)**	**P-value**
Age (yrs)[1]	68.3 (61.6-78.4)	70.5 (62.4-79.5)	69.4 (61.7-77.2)	67.1 (60.6-78.7)	0.882
Gender (Male)[2]	37 (48.7)	8 (32.0)	11 (42.3)	18 (72.0)	0.013
Weight (kg)[1]	75.0 (63.0-83.0)	65.0 (56.5-76.5)	72.5 (62.3-83.0)	80.0 (73.5-90.0)	0.003
BMI (kg/m^2)[1]	24.3 (21.9-26.0)	23.6 (21.1-25.5)	24.0 (21.4-25.3)	25.8 (23.5-28.4)	0.021
ASA score (ASA>2)[2]	5 (6.6)	1 (4.0)	1 (3.8)	3 (12.0)	0.465
Institutionalized pre-fracture[2]	1 (1.3)	0 (0.0)	0 (0.0)	1 (4.0)	0.356
Pre-fracture use of aids[2]	6 (7.9)	1 (4.0)	2 (7.7)	3 (12.0)	0.576
Subcapital fracture[2]	36 (47.4)	15 (60.0)	12 (46.2)	9 (36.0)	0.346
Displaced fracture (Garden III-IV)[2]	27 (35.5)	3 (12.0)	11 (42.3)	13 (52.0)	0.009
Pauwels class 3[2]	22 (28.9)	1 (4.0)	7 (26.9)	14 (56.0)	0.001
Time FNS measurements since surgery (months)[1]	11.7 (11.2-12.4)	11.7 (11.5-12.3)	11.5 (10.5-12.3)	11.8 (11.2-12.9)	0.448
Time gait measurements since surgery (months)[1]	22.3 (18.9-24.3)	22.9 (20.0-27.0)	22.0 (18.2-23.7)	21.5 (17.8-23.2)	0.187

FNS, Femoral Neck Shortening; BMI, Body Mass Index; ASA, American Society of Anesthesiologists. Differences between the three groups were tested with the Kruskal-Wallis ANOVA for continuous variables, and with the Chi-squared test for categorical variables.
[1] Data are presented as median with P_{25}-P_{75} given between brackets. [2] Data are presented as number with percentages.

Femoral neck shortening, gait pattern and muscular strength in the study population

The median femoral neck shortening was 1.1 cm (P_{25}-P_{75} 0.5-1.7). Forty percent of patients felt a leg length discrepancy, and scored their resulting complaints a median 4.0 on a VAS (P_{25}-P_{75} 1.5-7.2). Approximately one third of patients used a heel lift, with a median height of 1.0 cm (P_{25}-P_{75} 0.5-1.5). In 36% of the patients the implant had been removed because of implant-related complaints (Table 2).

The gait parameters differed by less than one percent between both legs, excepted stance time, which was 1.5% of the total gait cycle shorter for the fractured leg. The median gait velocity was 1.1 m/s P_{25}-P_{75} 0.9-1.2; Table 2). The average plantar pressure seemed reduced under metatarsals 1 and 2 (MT1 and MT2) and increased under the hallux, toes, and heel (Figure 2; $P>0.05$). Patients scored their satisfaction with their gait pattern a median 7.5 on a VAS (P_{25}-P_{75} 5.1-7.8).

The muscle strength of the flexor, extensor and adductor muscles decreased <10 N in the fractured leg compared with the contralateral side. The median decrease in strength for the abductor muscles was 20.9 N (P_{25}-P_{75} 0.0-35.1; Table 2).

At the time of the measurements 4% of the patients were institutionalized and 21% used an aid for mobilization (a 13% increase compared with the pre-fracture situation). Also, 18% of the patients still received physical therapy. The median SF-12 score was 102.1 (P_{25}-P_{75} 92.3-108.0) and the median WOMAC score was 86.5 (P_{25}-P_{75} 72.9-97.4; Table 2).

Table 2. Data on femoral neck shortening, gait parameters, muscle strength and self-reported patient functioning

	Total N=76	Little or none FNS (<0.75 cm) N=25	Moderate FNS (0.75-1.50 cm) N=26	Severe FNS (>1.50 cm) N=25	P-value
Femoral neck shortening (cm)[1]	1.1 (0.5-1.7)	0.4 (0.1-0.5)	1.1 (0.9-1.3)	2.0 (1.7-2.3)	<0.001
Feeling of LLD[2]	31 (40.8)	5 (20.0)	7 (26.9)	19 (76.0)	<0.001
VAS score complaints LLD[1]*	4.0 (1.5-7.2)	2.3 (0.5-7.1)	4.9 (4.8-8.0)	3.9 (1.9-7.0)	0.242
Heel lift use[2]	23 (30.3)	3 (12.0)	4 (15.4)	16 (64.0)	<0.001
Height Heel lift (cm)[1]**	1.0 (0.5-1.5)	0.5 (0.5-1.0)	0.8 (0.2-1.8)	1.2 (1.0-1.7)	0.161
Implant removed[2]	27 (35.5)	7 (28.0)	9 (34.6)	11 (44.0)	0.412
Weight distribution in stance (%)[1§]	0.5 (-5.5-5.4)	-0.5 (-5.3-5.2)	-0.7 (-7.4-5.4)	1.1 (-2.2-6.7)	0.439
Foot axis (°)[1§]	0.5 (-5.5-4.6)	2.4 (-1.2-7.4)	-2.8 (-7.3-3.9)	-1.8 (-6.5-4.8)	0.034
Stance time (% of gait cycle)[1§]***	-1.5 (-3.8--0.1)	-1.9 (-4.0--0.4)	-0.5 (-2.4-0.5)	-2.8 (-5.1--0.1)	0.116
Single support phase (% of gait cycle)[1§]***	-0.5 (-4.4-1.0)	-0.3 (-4.5-0.7)	0.1 (-3.7-1.8)	-3.0 (-5..4-0.5)	0.519
Double support phase (% of gait cycle)[1§]***	0.2 (-2.1-2.6)	0.4 (-0.6-1.1)	-0.5 (-2.6-3.5)	1.0 (-2.4-3.5)	0.806
Step length (cm)[1§]	0.0 (-3.2-3.8)	0.3 (-3.1-4.8)	0.0 (-2.7-3.6)	-0.5 (-3.4-3.4)	0.802
COP ΔY (cm)[1§]	0.5 (-7.9-6.9)	3.1 (-4.9-6.8)	0.5 (-8.0-7.7)	-4.4 (-11.6-9.8)	0.406
Gait velocity (m/s)[1]	1.1 (0.9-1.2)	1.1 (1.0-1.3)	1.1 (0.8-1.3)	1.0 (0.8-1.2)	0.165
VAS score satisfaction with gait pattern[1]	7.5 (5.1-8.7)	8.0 (6.5-9.0)	7.3 (5.3-8.3)	7.3 (4.3-8.0)	0.086
Flexion (N)[1§]	-1.3 (-13.5-3.9)	0.0 (-7.5-3.9)	-3.6 (-14.8-0.0)	-1.3 (-19.3-7.2)	0.474
Extension (N)[1§]	-3.9 (-27.6-13.7)	-6.5 (-32.7-13.1)	-4.2 (-18.4-8.7)	2.4 (-41.9-15.5)	0.701
Adduction (N)[1§]	-3.5 (-29.8-15.2)	-2.8 (-30.3-13.1)	-8.4 (-33.1-18.2)	-1.9 (-30.1-17.7)	0.891
Abduction (N)[1§]	-20.9 (-35.1-0.0)	-21.0 (-29.2-1.0)	-21.8 (-38.6-0.2)	-19.1 (-34.7--3.5)	0.934
SF-12 score[1]	102.1 (92.3-108.0)	102.4 (98.3-108.8)	101.7 (92.9-106.2)	99.8 (83.9-108.2)	0.439
WOMAC score[1]	86.5 (72.9-97.4)	95.6 (80.2-99.0)	88.5 (73.8-97.9)	81.2 (58.9-92.4)	0.059
Currently institutionalized[2]	3 (3.9)	1 (4.0)	1 (3.8)	1 (4.0)	0.999
Currently using aids [2]	16 (21.1)	4 (16.0)	4 (15.4)	8 (32.0)	0.261
Currently receiving physical therapy[2]	14 (18.4)	1 (4.0)	6 (23.1)	7 (28.0)	0.069

FNS, Femoral Neck Shortening; LLD, Leg Length Discrepancy; VAS, Visual Analog Scale; COP, Center of Pressure line; SF-12, Short Form 12; WOMAC, Western Ontario McMaster Osteoarthritis Index.

Differences between the three groups were tested with the Kruskal-Wallis ANOVA for continuous variables, and with the Chi-squared test for categorical variables.

[1] Data are presented as median with P_{25}-P_{75} given between brackets. [2] Data are presented as number with percentages.

* The VAS score for complaints as a result of a LLD was only measured in the 31 patients that indicated they the feeling of a LLD. ** The height of the heel lift was only measured in the 23 patients that used a heel lift. *** These variables had >10% missing data, because they require a completely measured gait cycle for both legs, which was often not feasible (Stance Time 13% missing and Single/Double Support Phase 61%).

§ The values displayed for these variables represent the difference between the two legs (Difference = Parameter $_{\text{fractured leg}}$ – Parameter $_{\text{contralateral leg}}$). A negative value therefore represents a decrease in the fractured leg, a positive value an increase.

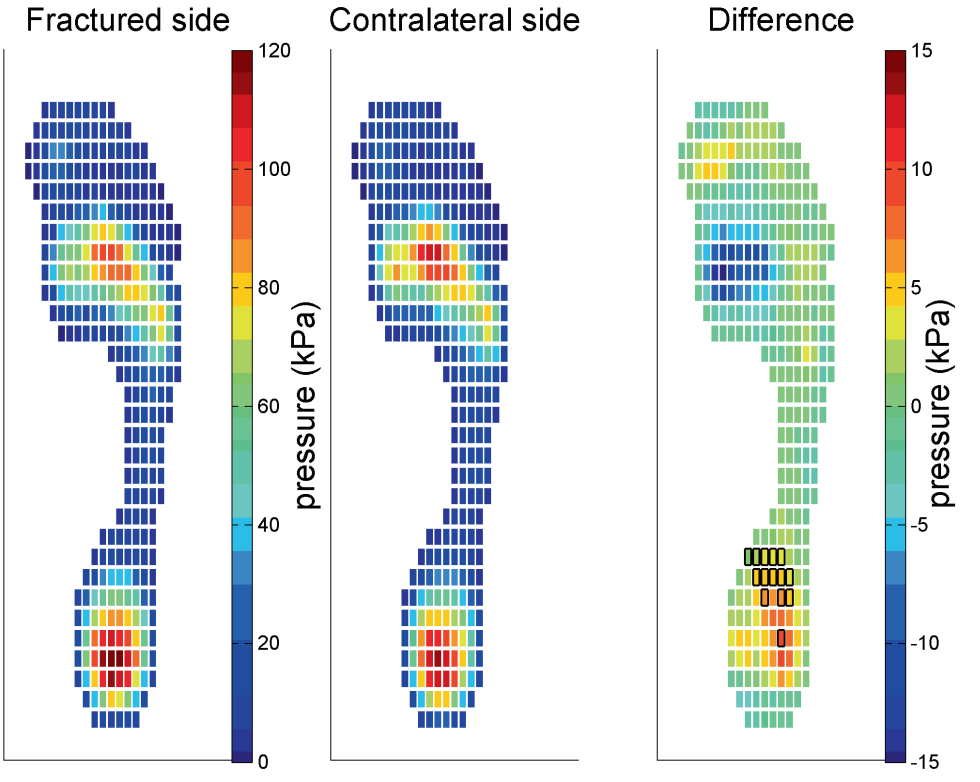

Figure 2. Average plantar pressure distribution
The left image shows the average plantar pressure distribution for the fractured side, the image in the middle shows the average plantar pressure distribution for the contralateral or control side. The right image shows the average difference in plantar pressure distribution between the two sides. A positive value indicates a higher pressure for the fractured leg in that square, a negative value indicates a lower pressure. The squares framed in bold indicate those sensors with significantly different changes in plantar pressure between the legs (P<0.05).

Risk factors for femoral neck shortening

Male gender and a higher weight were associated with an increased femoral neck shortening (32% male versus 42% versus 72%, P=0.013; median weight 65.0 kg versus 72.5 versus 80.0, P=0.003; Table 3). The same was found for a displaced fracture (Garden III-IV) and a Pauwels 3 fracture (12% displaced versus 42% versus 56%, P=0.009; 4% Pauwels 3 versus 27% versus 52%, P=0.001). In a multivariable regression model age, weight, and a Pauwels 3 fracture were independently associated with femoral neck shortening (Femoral neck shortening = -2.65 + (0.02 x age[year]) + (0.02 x weight[kg]) + (0.54 x Pauwels 3; Table 3).

Table 3. Regression coefficients for the factors that influence femoral neck shortening, gait velocity and WOMAC score

Determinant	Femoral neck shortening[1] beta (95% CI)	P-value	Gait velocity[2] beta (95% CI)	P-value	WOMAC score[3] beta (95% CI)	P-value
Constant	-2.65 (-4.60-- 0.70)	0.009	1.36 (0.86-1.85)	<0.001	50.62 (36.55-64.68)	<0.001
Age (years)	0.02 (0.00-0.04)	0.048	-0.01 (-0.01-0.00)	0.036		
Weight (kg)	0.02 (0.00-0.03)	0.012				
Pauwels 3	0.54 (0.20-0.88)	0.002				
Femoral neck shortening (cm)			-0.07 (-0.14--0.01)	0.034		
Current use of aids			-0.27 (-0.42--0.12)	0.001	-16.03 (-25.70--6.36)	0.001
Gait velocity (m/s)					17.87 (3.76-31.97)	0.014

Multivariable regression models using a backward stepwise approach
[1] Variables not in the equation: level of fracture, gender and Garden classification (undisplaced/displaced)
[2] Variables not in the equation: time since initial surgery, Garden classification (undisplaced/displaced) and gender
[3] Variables not in the equation: time since initial surgery, Garden classification (undisplaced/displaced), gender, femoral neck shortening, and age

Consequences of femoral neck shortening

Femoral neck shortening was associated with an increased feeling of leg length discrepancy (20% versus 27% versus 76%, P<0.001) and increased use of a heel lift (12% versus 15% versus 64%, P<0.001). More patients tended to have their implant removed if the femoral neck had shortened increasingly (28% versus 35% versus 44%, P>0.05).

None of the gait parameters were significantly different between the femoral neck shortening groups; heterogeneity across patients was high. Patients with severe femoral neck shortening tended to show an increased weight bearing on the fractured leg in stance (median increase 1.1% of total weight), a more endorotated foot axis (median axis -1.8°), a shorter stance time (median -2.8% of the gait cycle), a shorter single support phase and longer double support phase (median-3.0% and 1.0% of the gait cycle), a shorter step length (median-0.5 cm), a shorter center of pressure line (COP) (median-4.4 cm), and a lower gait velocity (median 1.0 m/s; Table 2). As femoral neck shortening increased, the pressure under the metatarsals tended to decrease, whereas the pressure under the hallux, toes, and heel of the fractured leg tended to increase (Figure 3). However, none of these trends reached statistical significance. As femoral neck shortening increased patient satisfaction with their gait pattern tended to decrease (median VAS score 8.0 versus 7.3 versus 7.3, P>0.05).

Muscle strength was not significantly different between the groups. In all groups the decrease in flexor, extensor and adductor muscles was <10 N in the fractured leg. The decrease in abductor strength was approximately 20 N in all groups (Table 2).

With an increased femoral neck shortening, a trend towards an increased use of aids for mobilization (16% versus 15% versus 32%; P>0.05) and a longer use of physical therapy (4% versus 23% versus 28%;, P>0.05) was seen. Similarly, the WOMAC tended to decrease (median WOMAC score 96 versus 89 versus 81, P>0.05; Table 2).

In a multivariable model, gait velocity was significantly associated with femoral neck shortening, age, and the use of aids for mobilization (Gait velocity[m/s] = 1.36 – (0.07 x femoral neck shortening[mm]) – (0.01 x age[year]) – (0.27 x use of aids for mobilization). The WOMAC score was influenced by the use of aids for mobilization and gait velocity, but was not significantly affected by femoral neck shortening (WOMAC score = 50.62 – (16.03 x use of aids for mobilization) + (17.87 x gait velocity[m/s]; Table 3).

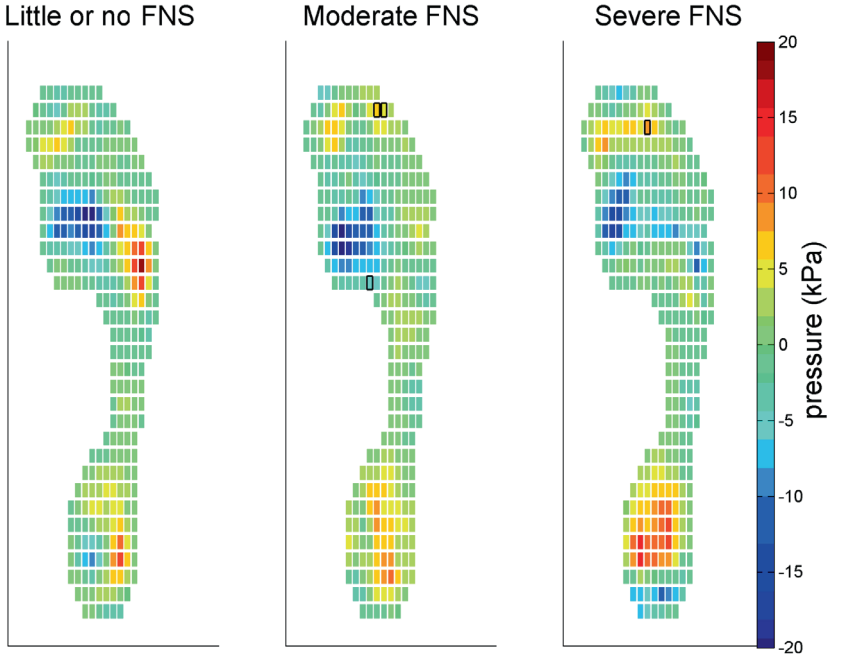

Figure 3. Differences in plantar pressure distribution between the fractured and contralateral leg for patients with various amounts of femoral neck shortening (FNS)
The left image shows the differences in plantar pressure distribution in the patients with little or no femoral neck shortening (<0.75 cm). The image in the middle shows the differences in plantar pressure distribution in the patients with moderate femoral neck shortening (0.75-1.50 cm). The right image shows the differences in plantar pressure distribution in the patients with severe femoral neck shortening (>1.50 cm). A positive value indicates a higher pressure for the fractured leg in that square, a negative value indicates a lower pressure. The squares framed in bold indicate those sensors with significantly different changes in plantar pressure between the legs (P<0.008; six groups of positive and negative sensors were compared, therefore threshold for significance = 0.05 / 6 = 0.008).

Discussion

Internal fixation of femoral neck fractures results in functional limitations, even after two years. In the studied population, the median femoral neck shortening at 22 months was 1.1 cm in the fractured leg. Over 50% of the patients healed with >1.0 cm shortening of the femoral neck, a shortening of >1.5 cm occurred in one third of our patients. This is a substantially higher percentage than the 30% healed with >1.0 cm shortening previously reported in a similar population.[13] The shortening caused complaints in 40% of patients and heel lift use in 30% of patients. Patients also had a reduced gait velocity (1.1 m/s (normal gait velocity 1.3-1.5 m/s)[20]) and subtle changes in the gait pattern. The abductor strength was reduced by 20N in the fractured leg, compared with the contralateral leg. The degree of shortening increased as patient age, weight and the Pauwels classification of the fracture increased. As all patients were permitted immediate weight bearing, healed without major complications or a need for revision surgery, and unite within a reasonable period of time it is not expected that any of these parameters significantly impacted gait and muscle strength.

Although none of the individual gait parameters reached statistical significance when comparing the femoral neck shortening groups, femoral neck shortening seemed to impair overall symmetry of gait. The increased double support phase and decreased stance phase in patients with severe shortening fit the characteristics of an abnormal gait pattern. Reaching statistical significance was hampered by a high heterogeneity across patients and subtle differences between the legs (often <1%). Although left-right differences in gait parameters were small, previous research has indicated that these subtle difference have clinical relevance.[21] The presence of a unilateral femoral neck fracture may also alter the gait characteristics of the contra-lateral intact limb to which it is being compared, influencing left-right differences.

Femoral neck shortening proved to have an independent negative influence on gait velocity in a multivariable comparison. Gait velocity is an important gait parameter that has proven to influence patient functioning, and is related to many other gait parameters.[22, 23] The correlation between impaired walking speed and reduced function scores in our patients confirms the importance of gait velocity as a predictor of patient function.

No information currently exists in the literature that contributes to interpreting the observed asymmetry in plantar pressure patterns. From a biomechanical perspective, the observed changes in the fractured leg could match a gait pattern with increased inversion of the foot (to compensate for a leg length discrepancy), or with enhanced stiffening in the first metatarso-phalangeal-joint. This gait mechanism can increase balance during walking, but is also influenced by gait velocity. In patients with severe shortening (>1.50 cm) a more flat gait pattern with decreased inversion and exorotation of the foot was seen (confirmed by the change in foot axis), and a decreased roll-of (confirmed by the shortening of the COP),

probably associated with a wider gait pattern. This could be due to the decreased abductor strength and balance as a result of the femoral neck shortening, and seems a more extensive compensatory mechanism to increase balance, but decreases gait economy. Consequently, patients with a severe femoral neck shortening tend to use more aids for mobilization and require longer use of physical therapy.

A trend existed towards a decreased patient functioning (SF-12 and WOMAC) with increased femoral neck shortening, but the association was less strong than that previously reported.[13] In general, patients had relatively high SF-12 and WOMAC scores, indicating good functioning. Coping strategies may play a role, indicated by the high SF-12 mental component score. Patients may have adapted their activities to their limitations, or were capable of developing sufficient compensatory strategies, because they were relatively young and healthy. Femoral neck shortening may affect older, more disabled patients to a larger extent, as they may be less capable of adapting. The results of this study should therefore not be generalized. There was no selection bias, as characteristics of the non-participating patients (*i.e.*, age, ASA-score and pre-fracture use of aids) did not differ significantly from those in the included population. To promote adaption and coping, patients should be informed about the expected long-term limitations as early as possible. Surgeons could even consider a primary arthroplasty in high-risk patients, taking the risk-factors for femoral neck shortening into account (*i.e.;* age, weight and Pauwels classification).

The consequences of femoral neck shortening can be partially compensated through the use of a heel lift. There was a low observed incidence of heel lift use (30% in the overall group, 64% in the severe shortening group). Out of 31 patients that indicated discomfort resulting from a leg length discrepancy 32% did not have a heel lift. Physicians should therefore pay more attention to femoral neck shortening after internal fixation of a femoral neck fracture, and consider the option of a heel lift with all patients.

The current study is the first attempt to quantify gait characteristics in relation to femoral neck shortening following a femoral neck fracture. This study has several limitations. The effect of osteoporosis on femoral neck shortening could not be determined as osteoporosis data were unavailable. However, following the study treatment protocol, all patients were screened for osteoporosis and treated if necessary. Because available X-rays were used, taken in different rotational angles, the abductor moment arm shortening could not be measured reliably. Secondly, gait was measured over a relatively narrow force measurement plate of 40 cm, which compromised a reliable measurement of gait width. Finally, gait parameters and plantar pressure patterns do not only reflect changes in the hip, but can be influenced by many factors throughout the kinetic chain. Future studies should combine force and pressure measurements with video assessment since the latter may help interpreting the kinetic data.

Conclusion

Internal fixation of a femoral neck fracture results in femoral neck shortening in the majority of patients. It also results in several long-term physical limitations. Femoral neck shortening impairs gait velocity and causes complaints in some patients. The degree of shortening increases with patient age, weight and the Pauwels classification. The relatively young and healthy population included in this study seems capable of compensating for these limitations. However, attention should be paid to adequate compensation of a shortened femoral neck and patients should be informed about the consequences as early as possible. Surgeons could even consider a primary arthroplasty in high-risk patients. Future studies should consider patient-reported functioning and include objective functional outcome measurements, particularly femoral neck shortening, muscle strength and gait velocity, because these are more specific.

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Chapter 8

Functional outcome after successful internal fixation versus salvage arthroplasty of patients with a femoral neck fracture

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Abstract

Objectives: To determine patient independency, health-related and disease-specific quality of life (QOL), gait pattern, and muscle strength in patients after salvage arthroplasty for failed internal fixation of a femoral neck fracture.

Design: Secondary cohort study to a randomized controlled trial.

Setting: Multicenter trial in the Netherlands, including 14 academic and non-academic hospitals

Patients: Patients after salvage arthroplasty for failed internal fixation of a femoral neck fracture were studied. A comparison was made with patients who healed uneventfully after internal fixation.

Intervention: None (observatory study)

Main outcome measurements: Patient characteristics, SF-12, and WOMAC scores were collected. Gait parameters were measured using plantar pressure measurement. Maximum isometric forces of the hip muscles were measured using a handheld dynamometer. Differences between the fractured and contralateral leg were calculated. Groups were compared using univariate analysis.

Results: Of 248 internal fixation patients (median age 72 years), salvage arthroplasty was performed in 68 patients (27%). Salvage arthroplasty patients had a significantly lower WOMAC score (median 73 versus 90, P=0.016) than patients who healed uneventfully after internal fixation. Health-related QOL (SF-12) and patient independency did not differ significantly between the groups. Gait analysis showed a significantly impaired progression of the center of pressure in the salvage surgery patients (median ratio-8.9 versus 0.4, P=0.013) and a significant greater loss of abduction strength (median-25.4 versus-20.4 N, P=0.025).

Conclusion: Despite a similar level of dependency and QOL, salvage arthroplasty patients have inferior functional outcome than patients who heal after internal fixation of a femoral neck fracture.

Introduction

The optimal surgical treatment of femoral neck fractures remains unclear.[1-5] Treatment options are internal fixation, arthroplasty, and in specific cases conservative treatment. Revision surgery rates of approximately 35% have been reported after internal fixation failure.[1, 3-5] It has been argued that salvage arthroplasty is a safe procedure if internal fixation fails, and that surgical outcome of salvage arthroplasty is satisfactory.[6-8] However, little is known about the functional outcome after salvage arthroplasty for failed internal fixation of a femoral neck fracture. Few studies have focused on functional outcome, and have only recorded general function such as walking ability and pain or general health-related quality of life scores.[8-12] To the best of our knowledge, a disease-specific functional score was used only in two studies.[10, 13] Objective functional outcome parameters such as muscle strength or gait are not available, even though they are important factors influencing walking ability and quality of life. Gait analysis may add information to the results from functional outcome scores like the Western Ontario McMaster Osteoarthritis Index (WOMAC).[14] Its value has been proven in clinical studies of other surgical interventions, such as hip arthroplasty for degenerative osteoarthritis.[15]

The aim of this study was to determine traditional outcome parameters such as patient independency and health-related quality of life (QOL) as well as disease-specific QOL, gait pattern, and muscle strength in patients after salvage arthroplasty for failed internal fixation of patients with a femoral neck fracture. The study was performed as a secondary cohort study to the Dutch sample of an international randomized controlled trial, the FAITH trial. Results of salvage arthroplasty patients were compared with those of patients that did not receive a salvage arthroplasty. We hypothesized that patients after salvage arthroplasty would have worse functional outcome and QOL than patients that did not receive a salvage arthroplasty.

Patients and Methods

Population

This study (clinical trial registration number, NL32419.078.10) was a secondary cohort study to the Dutch sample of an international randomized controlled trial, the FAITH trial (Fixation using Alternative Implants for the Treatment of Hip fractures, NCT00761813). The primary objective of the FAITH trial was to assess the impact of internal fixation implants (sliding hip screw versus multiple cancellous screws) on rates of revision surgery at two years in elderly patients with femoral neck fractures. In the Netherlands 14 hospitals participated and randomized 250 patients between February 2008 and August 2009. These patients were adults aged >50 years, who were ambulatory and not cognitively impaired pre-fracture.

Patients had an undisplaced fracture or a displaced fracture (in ASA 1-2 patients, aged 50-80 years, with a fracture that could be reduced closed).[16] Surgeries were performed or supervised by a senior surgeon. All patients were allowed weight bearing as tolerated after initial surgery.[17]

In the current study, all Dutch FAITH patients who received a salvage arthroplasty (for any reason, *e.g.,* avascular necrosis, non-union, internal fixation break-out, or persisting pain) were compared with patients who healed after internal fixation (control group). The decision to plan a re-operation was left to the discretion of the treating surgeon. Surgeons used their preferred approach and type of prosthesis, which therefore varied (both unipolar and bipolar). In a sub-study gait pattern and muscle strength were measured. Patients were included in the gait analysis at least one year after their initial internal fixation surgery. Exclusion criteria were:

- Primary conversion to arthroplasty
- Not capable of walking several meters independently
- Lower limb abnormalities that could be expected to influence gait pattern
- Previous internal fixation or arthroplasty of the contralateral (control) hip.

Salvage surgery patients in the gait analysis were compared with a control sample of patients from the Dutch FAITH population who did not have salvage arthroplasty, but healed after internal fixation. Gait pattern and muscle strength in the control group had been measured in a previously published study, using the same selection criteria and study protocol.[18] The study was approved by the Medical Research Ethics Committee (MEC-2010-164).

Data and measurements

Patient and fracture characteristics at the time of the fracture, and surgical characteristics, rehabilitation data, Western Ontario McMaster Osteoarthritis Index (WOMAC) and Short Form-12 (SF-12) scores at two years follow-up were available from the FAITH trial.[19, 20] SF-12 scores were converted to a norm-based score and compared with general population norms of the United States (1998), as weighing factors for the Dutch population were not available.

Measurements of gait pattern and muscle strength were performed during a single visit to the outpatient clinic, following the same protocol applied previously.[18] Gait analysis was performed using a pressure plate (Footscan®, RSscan International, Olen, Belgium; 2.0 x 0.4m, 125 Hz). Patients were instructed to walk barefoot across the pressure plate at their usual, preferred speed, starting several steps before and ending several steps after the pressure plate. Five measurements were performed per patient. The combination of at least three gait measurements that were most representative for each patient were selected based upon the coefficient of variation, and used for analysis. The following temporospatial gait parameters were analyzed: gait velocity, duration of stance phase, single and double support phase, step length, foot axis, and progression of the center of pressure in the walking direction (COP

ΔY). Data of the fractured leg were compared with the contralateral side. The difference was computed using the formula: Parameter $_{\text{fractured leg}}$ – Parameter $_{\text{contralateral leg}}$.

The maximum isometric forces of the hip muscles were measured using a handheld dynamometer (MicroFET®, Biometrics BV, Almere, the Netherlands). Flexion, extension, abduction, and adduction strength were measured in a supine position. The means of triplicate measurements were calculated, and the differences between the affected extremity and control side were computed.

Finally, leg length was measured during the visit, using a direct tape measure method. The distance between the anterior superior iliac spine and the medial malleolus was measured twice. The average value was used for analysis. This strategy has an acceptable validity and reliability.[21] Patients were also asked if they felt they had a leg length discrepancy. If so, patients completed a Visual Analog Scale (VAS) to indicate how much they felt hampered due to the discrepancy. The VAS ranged from zero (free of complaints) to ten (very much hampered). Use of a heel lift to correct a leg length discrepancy was also recorded. Finally, patient satisfaction with their gait pattern was measured using a VAS, ranging from zero (extremely dissatisfied) to ten (completely satisfied).

Data analysis

Analyses were performed using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA). Because this was an explorative cohort study in a restricted sample of patients, statistical analysis was confined to univariate comparison of patients who received salvage arthroplasty with patients who healed after internal fixation (control group). For continuous variables the Mann-Whitney U-test was used, and the Chi-squared test or Fisher's exact test for categorical variables. Results with $P<0.05$ (two-sided test) were regarded as statistically significant. Continuous variables, which were all non-parametric, are presented as medians with interquartile ranges. Categorical variables are presented as numbers and percentages.

Results

Patient, fracture, and treatment characteristics

Of the initial group of 250 randomized patients, two patients could not be followed; one patient turned out not to have a femoral neck fracture and one patient withdrew consent immediately after randomization. Patient, fracture, and treatment characteristics of the remaining 248 patients are shown in Table 1. The study group had a median age of 72 years (P_{25}-P_{75} 62-78). Patients were relatively healthy and independent pre-fracture. Prior to the fracture only 3% of the patients were institutionalized and 13% used an aid for mobilization. Thirteen percent had severe comorbidities (ASA3). The median follow-up was 26 months (P_{25}-P_{75} 25-28) after the initial surgery.

Table 1. Patient, fracture, and treatment characteristics

	Salvage arthroplasty (HA/THA) (N=68)	Internal Fixation (N=164)	P-value
Age (years)[1]	72 (66-79)	70 (62-78)	0.301
Males[2]	21 (31)	73 (45)	0.058
BMI (kg/m^2)[1]	24 (22-27)	24 (22-26)	0.151
ASA score 3[2]	8 (12)	23 (14)	0.329
Institutionalized pre-fracture[2]	4 (6)	3 (2)	0.199
Pre-fracture use of walking aids[2]	11 (16)	21 (13)	0.533
Displaced fracture (Garden III-IV/AO 31-B2-3) [2]	42 (62)	57 (35)	<0.001
Pauwels 3[2]	35 (52)	42 (26)	<0.001
Implant removed[2]	N.A.	38 (23)	N.A.
Revision to THA[2]	45 (66)	N.A.	N.A.
Time since last surgery (months)[1*]	21 (15-24)	25 (24-28)	<0.001
Follow-up duration (months)[1]	26 (25-28)	26 (25-28)	0.762

HA, Hemiarthroplasty; THA, Total Hip Arthroplasty; BMI, Body Mass Index; ASA, American Society of Anesthesiologists; N.A., not applicable.
Differences between groups were tested with the Mann-Whitney U-test for continuous variables, and with the Chi-squared test or Fisher's exact test for categorical variables.
[1] Data are presented as median with P_{25}-P_{75} given between brackets. [2] Data are presented as number with percentages.
*This parameter reflects the time since the last surgery (*i.e.,* either the primary internal fixation, the implant removal, or the salvage arthroplasty procedure).

Salvage arthroplasty was performed in 68 patients (27%), of whom 45 (66%) received a total hip arthroplasty. Patients who received a salvage total hip arthroplasty were significantly younger than patients who received a salvage hemi-arthroplasty (median age 70 versus 76 years, P=0.035). The total hip arthroplasty patients were also more independent in their functioning pre-fracture (0% versus 17% living institutionalised, P=0.011, 9% versus 30% use of walking aid, P=0.036)

Of the 180 patients who healed after internal fixation 38 patients (21%) had their implant removed during the follow-up, mainly because of painful hardware. Taking all revision surgeries into account, there was a significantly shorter time between last surgery and final follow-up in the salvage arthroplasty patients than in the patients who healed after internal fixation (median 21 versus 25 months, P<0.001).

Salvage arthroplasty was performed more frequently after a displaced fracture (Garden III-IV/AO 31-B2-3); 62% in the salvage arthroplasty group versus 35% in the healed after internal fixation group; P=0.001) or a Pauwels III fracture (52% versus 26%, P=<0.001).[22] Of all undisplaced fractures (Garden I-II/AO 31-B1) 20% failed, whereas 42% of all displaced fractures failed. Other characteristics were similar in both groups (Table 1).

Patient independency, health-related and disease-specific quality of life (QOL)

Health-related quality of life and patient independency did not differ significantly between the patients who healed after internal fixation and the salvage arthroplasty patients. There was no significant difference in SF-12 score, rates of institutionalization, the ability to walk independently, or the use of physical therapy at two years follow-up (Table 2). However, the salvage arthroplasty patients reported significantly lower median WOMAC scores at two years follow-up than the patients that healed after internal fixation (73 versus 90 points, P=0.016). This difference was mainly seen in the functional domain of the questionnaire, and to a lesser extent in the pain and stiffness domain. The salvage arthroplasty patients also reported a significant longer total use of physical therapy (median 26 weeks versus 11 weeks in the group healed after internal fixation; P=0.002). No significant differences in independency and QOL scores were found when comparing hemi-arthroplasty patients with total hip arthroplasty patients in the salvage group.

Table 2. Patient independency, health-related and disease-specific quality of life (QOL)

	Salvage arthroplasty (HA/THA) (N=68)	**Internal Fixation (N=164)**	**P-value**
SF-12 score[1]	93 (82-109)	99 (86-109)	0.347
WOMAC score[1]	73 (56-94)	90 (71-97)	0.016
Currently institutionalized[2]	10 (18)	18 (12)	0.550
Currently using walking aids[2]	29 (52)	58 (39)	0.113
Currently receiving physical therapy[2]	12 (21)	26 (19)	0.546
Duration of physical therapy (weeks)[1a]	26 (12-55)	11 (6-28)	0.002

HA, Hemiarthroplasty; THA, Total Hip Arthroplasty; SF-12, Short Form 12; WOMAC, Western Ontario McMaster Osteoarthritis Index

Differences between groups were tested with the Mann-Whitney U-test for continuous variables, and with the Chi-squared test or Fisher's exact test for categorical variables.

[1] Data are presented as median with P_{25}-P_{75} given between brackets. [2] Data are presented as number with percentages.

[a] Data on the duration of the physical therapy were only collected in the 96 patients that participated in the gait analysis study

Gait analysis, muscle strength and leg length discrepancy

Of the 68 salvage arthroplasty patients, 47 were eligible to study gait pattern and muscle strength, following the inclusion and exclusion criteria for this study (Figure 1). Nineteen patients gave informed consent. The patient characteristics of the 28 patients that did not want to participate (*i.e.*, age, ASA-score and pre-fracture use of aids) did not differ significantly from those in the included population. The included patients were compared with a control group of 77 patients who healed after internal fixation (Figure 1). Characteristics of these two subgroups of 19 and 77 patients were similar as the characteristics summarized in Table 1 for the total groups.

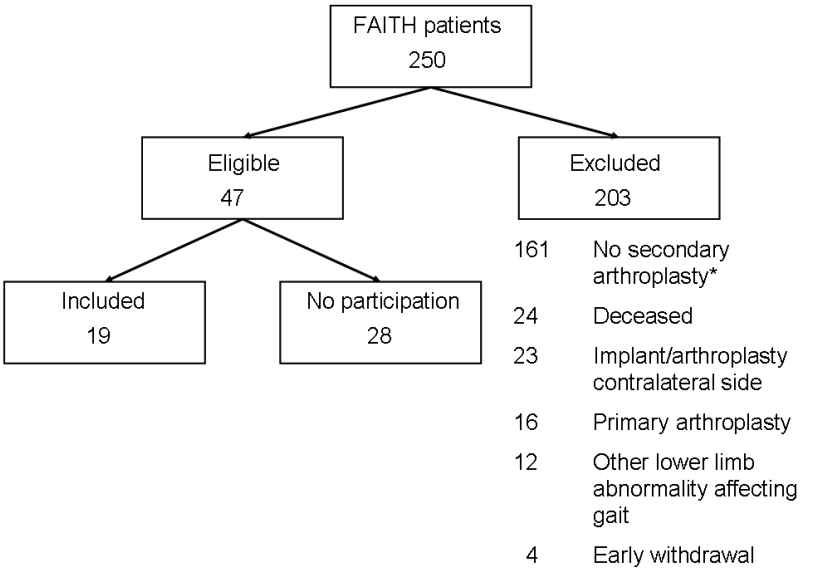

Figure 1. Flowchart of salvage arthroplasty patients participating in the gait analysis study
* The 77 patients in the control group (*i.e.,* patients who healed after internal fixation) were selected and included from this subgroup.

The gait parameters did not differ statistically significantly between the groups, except for the progression of the center of pressure in the walking direction (COP ΔY; Table 3). The COP is a parameter indicating the degree and direction of roll-off of the foot. The progression of the COP reflects the transfer of load from the left to the right limb and vice versa. The COP progression in the walking direction was significantly decreased for the fractured leg in the salvage arthroplasty patients, whereas an increase was noted in the patients who healed after internal fixation (median ratio -8.9 versus 0.4, P=0.013). Median gait velocity was 1.1 m/s in both groups. Patient scored their satisfaction with gait pattern a median of 7.4 on a VAS, which did not differ significantly between the groups.

Salvage arthroplasty patients had a significantly greater loss of abduction strength in the fractured leg than patients who healed after internal fixation did (median -25.4 versus -20.4 N, P=0.025; Table 3). Finally, the leg length discrepancy was less in the salvage arthroplasty patients than in patients who healed after internal fixation (median 0.0 versus 0.8 cm, P=0.001). Consequently, they used a heel lift less often (5% versus 30%, P=0.036).

Table 3. Gait analysis, muscle strength, and leg length discrepancy

	Salvage arthroplasty (HA/THA) (N=19)	Internal Fixation (N=77)	P-value
Gait velocity (m/s)[1]	1.0 (0.6-1.2)	1.2 (1.1-1.5)	0.413
Stance time (% of gait cycle)[1§b]	-1.8 (-5.2-0.1)	-1.6 (-3.8--0.1)	0.446
Single support phase (% of gait cycle)[1§b]	-2.2 (-4.0--0.2)	-0.5 (-4.4-1.0)	0.554
Double support phase (% of gait cycle)[1§b]	-0.3 (-1.7-1.1)	0.2 (-2.1-2.6)	0.545
Step length (cm)[1§]	1.8 (-1.5-4.1)	0.0 (-3.2-3.8)	0.249
Foot axis (°)[1§]	-2.3 (-10.2-9.0)	0.6 (-5.1-4.9)	0.402
COP ΔY (cm)[1§]	-8.9 (-13.0--1.8)	0.4 (-8.1-6.8)	0.013
VAS score satisfaction with gait pattern[1]	7.1 (4.7-8.5)	7.4 (5.0-8.7)	0.847
Flexion (N)[1§]	-18.6 (-41.1-9.3)	-1.3 (-13.5-4.1)	0.108
Extension (N)[1§]	-14.1 (-37.5-6.2)	-3.5 (-26.9-13.2)	0.226
Adduction (N)[1§]	-6.9 (-26.0-11.6)	-2.8 (-29.3-19.0)	0.713
Abduction (N)[1§]	-25.4 (-67.5--17.8)	-20.4 (-35.0-0.7)	0.025
LLD (cm)[1]	0.0 (-0.8-1.0)	0.8 (0.3-1.8)	0.001
Feeling of LLD[2]	3 (16)	31 (40)	0.061
VAS score complaints LLD[1a]	4.9 (2.6-6.0)	4.0 (1.5-7.2)	0.813
Heel lift use[2]	1 (5)	23 (30)	0.036

HA, Hemiarthroplasty; THA, Total Hip Arthroplasty; LLD, Leg Length Discrepancy; VAS, Visual Analog Scale; COP, Center of Pressure line

Differences between groups were tested with the Mann-Whitney U test for continuous variables, and with the Chi-squared test or Fisher's exact test for categorical variables.

[1] Data are presented as median with P_{25}-P_{75} given between brackets. [2] Data are presented as number with percentages.

[a] The VAS score for complaints as a result of a LLD was only measured in the 34 patients that indicated having the feeling of a LLD. [b] These variables had >10% missing data, because they require a completely measured gait cycle for both legs, which was often not feasible (Stance Time 14% missing and Single/Double Support Phase 54%).

[§] The values displayed for these variables represent the difference between the two legs (Parameter $_{\text{fractured leg}}$ – Parameter $_{\text{contralateral leg}}$).

A negative value therefore represents a decrease in the fractured leg, a positive value an increase.

Discussion

Salvage arthroplasty resulted in inferior disease-specific functional outcome scores (WOMAC) than successful internal fixation did. Twenty-seven percent of patients required salvage arthroplasty after internal fixation of a femoral neck fracture. This is in line with previously published data, both for the percentage failure in displaced fractures (37%) and undisplaced fractures (19%).[1, 4, 5] To the best of our knowledge, functional outcome of salvage surgery patients has never previously been compared with outcome of patients who healed uneventfully after internal fixation. However, Blomfeldt et al. showed a worse functional outcome of salvage arthroplasty after failed internal fixation compared with primary arthroplasty.[10]

The observed inferior disease-specific functional outcome scores did not lead to a difference in health-related quality of life. With a median SF-12 score of 93 points, salvage arthroplasty patients seemed to have a good health-related quality of life. This may reflect a good coping mechanism of the relatively young and healthy femoral neck fracture study population. It also demonstrates that functional outcome after hip surgery should be tested with a disease specific questionnaire, because generic questionnaires like the SF-12 may not be specific enough.

A more deviant gait pattern may contribute to the inferior functional outcome in patients after salvage arthroplasty. In our study group, salvage arthroplasty patients had a more impaired progression of the center of pressure in the fractured leg, indicating an impaired transfer of load underneath the affected limb. This could be the effect of impaired balance, or, as indicated by the univariate analysis, an overall impaired muscle strength of the hip abductor muscles in the affected limb.[23] None of the other individual gait parameters reached statistical significance when comparing the groups. Perhaps with increasing numbers, more significant alterations in gait pattern may be measured in the salvage arthroplasty patients. Moreover, although the left-right differences in gait parameters seem small, research in patients after total hip arthroplasty for osteoarthritis has indicated that these subtle difference have clinical relevance.[24]

Another contributing factor to the inferior functional outcome in patients after salvage arthroplasty is a greater loss of abductor muscle strength. The median loss of 25 N can be expected to have clinical relevance. This greater loss of strength in the salvage arthroplasty patients can be explained by the need to recover from multiple surgeries and an additional incision and exposure for the arthroplasty (which is more extensive than for internal fixation, depending on the type of prostheses and the surgical approach).This extra surgery causes more damage to the underlying tissue, mainly the abductor muscles. Furthermore, these patients have often suffered from a period of pain and limping, and have been hampered in their rehabilitation process preceding the salvage surgery, mainly caused by the primary reason of the salvage arthroplasty (usually avascular necrosis or non-union/implant break-out). Our results show that the re-operation cannot salvage the functional level following a long period with a suboptimal internal fixation. In accordance, salvage surgery patients may benefit from more specific rehabilitation programs aimed at improving hip muscle strength (*e.g.* gait assisted functional electro stimulation).

The inferior functional outcome of salvage arthroplasty patients in the current study and in the study by Blomfeldt *et al.* suggests that patients receiving internal fixation of a femoral neck fracture should be selected very carefully. The notion that salvage arthroplasty is a safe procedure if internal fixation fails, should perhaps be reconsidered with caution. This aspect should receive more attention as previous studies suggest little difference in functional outcome.[6, 8] In the current study, patients receiving a salvage arthroplasty more

frequently had a displaced fracture classification (both Garden and Pauwels). As such, our data suggest that surgeons could more liberally consider a primary arthroplasty for patients with displaced (Garden III-IV), sheer (Pauwels 3) femoral neck fractures.[16] However, further research comparing functional outcome in patients after primary and salvage arthroplasty should render more evidence on this matter.

Our data do not suggest superiority of any type of arthroplasty over the other, as patients treated with salvage hemi-arthroplasty and total hip arthroplasty had similar patient independency and quality of life scores. Surgeons do seem to take patient characteristics into account when deciding on type of arthroplasty, as salvage total hip arthroplasty patients were significantly younger and more independent in their functioning pre-fracture.

The main limitation of this study is the restricted number of included patients in the secondary gait analysis study. Multivariable analyses were not feasible. Selection bias seems unlikely, as the patient characteristics of the 28 patients that did not participate did not differ significantly from those in the included population. Due to a limited number of patients in the salvage arthroplasty group it was not possible to perform subgroup analyses by surgical approach or type of prosthesis. A larger sample size is needed in order to perform more detailed analyses on the factors that contribute to the inferior functional outcome of salvage surgery patients.

A second limitation is the difference in time since last surgery between the study groups, indicating that the study groups may not have been completely comparable. However, the median time since last surgery was >20 months in both groups. The functional progression that can be expected after that time period is limited. This difference will therefore probably have only very limited influence on the results of this study.

The population in the current study consisted of relatively young and healthy persons; demented patients and patients unsuitable for internal fixation were excluded. The results of this study should therefore not be generalized to all hip fracture patients,

In conclusion, patients requiring salvage arthroplasty after initial internal fixation of a femoral neck fracture have inferior functional outcome than patients who healed after internal fixation. A greater loss of muscle strength and a more deviant gait pattern may have contributed to this. Despite lower functional outcome scores, these patients do not have a worse health-related quality of life, probably caused by an adequate coping mechanism of our relatively young and healthy study population. When considering internal fixation for fitter femoral neck fracture patients the possibility of a salvage arthroplasty must be acknowledged and patients can be informed about slightly lesser functional outcome.

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Chapter 9

Implant removal after internal fixation of a femoral neck fracture: effects on physical functioning

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Abstract

Objectives: The effect of implant removal after internal fixation of a femoral neck fracture on physical functioning was analyzed. Characteristics of patients who had their implant removed were studied, as it is currently unknown in which type of patients implants are removed and what effect removal has on function.

Design: Secondary cohort study alongside a RCT.

Setting: Multicenter study in 14 hospitals.

Patients and Intervention: Patients who had their implant removed after internal fixation of a femoral neck fracture are compared with patients who did not.
Main outcome measurements: Patient characteristics and quality of life (Short Form-12 (SF-12), Western Ontario McMaster Osteoarthritis Index (WOMAC)) were compared. Matched pairs were selected based on patient/fracture characteristics and pre-fracture physical functioning.

Results: Of 162 patients, 37 had their implant removed (23%). These patients were younger (median age 67 versus 72 years, P=0.024) and more often independently ambulatory pre-fracture (100% versus 84%, P=0.008) than patients who did not. They more often had evident implant back-out on X-rays (54% versus 34%, P=0.035), possibly related to a higher rate of Pauwels 3 fractures (41% versus 22%, P=0.032). In time, quality of life improved more in implant-removal patients (+2 versus-4 points SF-12 (physical component), P=0.024; +9 versus 0 points WOMAC, P=0.019).

Conclusions: Implant removal after internal fixation of a femoral neck fracture positively influenced quality of life. Implant-removal patients were younger and more often independently ambulatory pre-fracture, more often had a Pauwels 3 fracture, and an evident implant back-out. Implant removal should be considered liberally for these patients if pain persists or functional recovery is unsatisfactory.

Introduction

Internal fixation of femoral neck fractures can sometimes result in long-term physical limitations and pain, even if fractures have healed uneventfully.[1] These limitations can be caused by physical changes such as tissue damage, scarring, and loss of muscle strength due to the injury and surgical exposure, or femoral neck shortening due to impaction at the fracture site.[1] The implant can cause local irritation and functional impairment.[2-4] In some patients with persistent complaints the implant is therefore removed after fracture healing. The rate of implant removal after internal fixation of femoral neck fractures is unknown. Reported implant removal rates after internal fixation of fractures at various anatomical locations including the hip, ranges from 16% to 81%.[5,6]

Guidelines on when to remove implants do not exist, mainly due to a lack of evidence. Several surveys among surgeons have indicated that patient related factors (*e.g.,* local irritation, pain, (unexplained) complaints, or patients request), possible carcinogenic/toxic, or unknown systemic effects, and expected problems with later removal due to bony overgrowth are considered reasons for implant removal.[2-4,7] A greater risk of future fractures due to stress shielding may also be a reason.[8,2,4] General reasons not to remove implants could be the risk of tissue or nerve damage, or an adverse event (mainly wound infection or hematoma) associated with secondary surgery. The costs of a second surgery and rehabilitation period may also play a role. Two cohort studies have indicated that removal of implants, at various anatomical locations, improves pain relief and function.[9,10] In other studies, however, the relief of complaints was not found.[11,2,7]

To the best of our knowledge, implant removal after internal fixation of femoral neck fractures has not been reported in detail. The effect of implant removal on physical functioning in these patients is therefore unknown. It is also unknown which patients are candidates for removal. Therefore, the aim of this study was to analyze the effect of implant removal after internal fixation of a femoral neck fracture on physical functioning. Characteristics of patients who had their implant removed were also described.

Patients and Methods

Population

This study was a secondary cohort study to the Dutch sample of an international randomized controlled trial, the FAITH trial (Fixation using Alternative Implants for the Treatment of Hip fractures, NCT00761813).[12] The primary objective of the FAITH trial was to assess the impact of internal fixation implants (sliding hip screw versus multiple cancellous screws) on rates of revision surgery at two years in elderly patients with femoral neck fractures (*i.e.,* AO type 31-B fractures).[13] In the Netherlands 14 hospitals participated and randomized 250

patients between February 2008 and August 2009. These patients were adults aged >50 years, who were ambulatory and not cognitively impaired pre-fracture. Patients had either (a) an undisplaced fracture, or (b) a displaced fracture in ASA 1-2 patients, who were 50-80 years old, with a fracture that could be reduced closed.[14] Surgeries were either performed or supervised by an experienced surgeon. All patients were allowed weight bearing as tolerated after surgery.

In the current study, all Dutch FAITH patients who healed after internal fixation were studied. Patients who had their implant removed were compared with patients who did not (control group). Patients who had a revision surgery due to implant failure, non-union, or avascular necrosis (*i.e.,* implant switch or salvage arthroplasty) were excluded. Patients who had a primary arthroplasty due to an unsuccessful fracture reduction were also excluded. The indication for implant removal was persisting pain and/or functional limitation in various degrees, which was considered to be (possibly) caused by the implant. The decision to remove the implant was left to the discretion of the treating surgeon. The implant was removed approximately one year after the fracture surgery if the fracture had healed.

Data and measurements

Patient baseline characteristics, fracture characteristics, and follow-up data, including health-related quality of life (Short Form-12 (SF-12)) and disease-specific quality of life scores (Western Ontario McMaster Osteoarthritis Index (WOMAC)) were available from the FAITH trial.[15,16] In order to calculate the baseline (*i.e.,* pre-fracture) score, patients completed the questionnaires asking for their pre-fracture quality of life within one week after the fracture. SF-12 scores were converted to a norm-based score and compared with the norms for the general population of the United States (1998), as weighing factors for the Dutch population were not available.

X-rays were also collected. In order to study the relation between implant back-out and implant removal, a single investigator scored all X-rays for signs of 'evident implant back-out'. This was defined as back-out with evident increasing distance of the distal end of the implant in relation to the lateral femoral cortex (Figure 1).

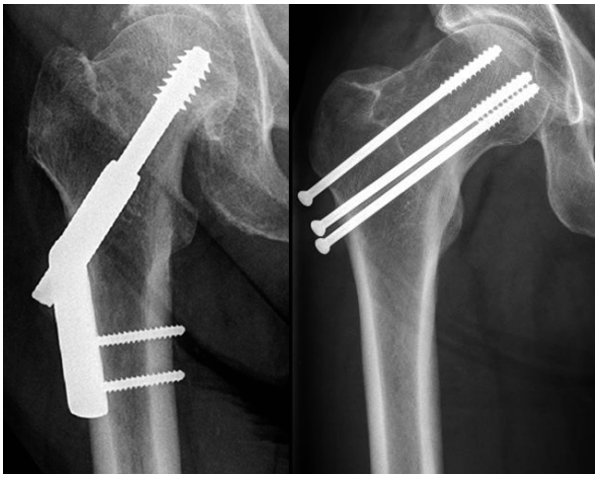

Figure 1. Example of evident implant back-out

Statistical analysis

Analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 16.0, SPSS Inc., Chicago, IL, USA).Baseline and fracture characteristics, as well as SF-12 and WOMAC scores at baseline (*i.e.,* pre-fracture) and after two years follow-up were compared. The change in scores between these two moments was calculated using the formula: Change Score = $\text{Score}_{\text{2 years}} - \text{Score}_{\text{baseline}}$. Continuous data are presented as medians with percentiles, categorical variables as numbers and percentage. In the crude analysis, groups were compared using a Mann Whitney U-test (continuous data) or a Chi-squared test (categorical data).

In order to study the effect of implant removal on patient functioning more specifically, a matched pair analysis was performed. A matched control was searched for all implant removal patients with complete follow-up data. Controls were considered adequate if they had a comparable age (<5 years difference), identical ASA score (American Society of Anesthesiologists classification), pre-fracture living status, pre-fracture use of ambulatory aids, fracture classification (Garden I/II versus III/IV and Pauwels 1-2 versus Pauwels 3), type of implant, and a comparable WOMAC score at baseline (<5 points difference). Use of a single control for multiple patients was allowed. In the matched pair analysis, SF-12 and WOMAC scores for the implant removal patients were calculated for the follow-up moment immediately before implant removal (mostly 12 or 18 months after initial fracture surgery) and at the first follow up moment after removal (mostly 18 or 24 months after initial fracture surgery). For the matched control the scores at the same follow-up moment in time were used. The change in scores between these two moments was calculated using the formula: Change Score = $\text{Score}_{\text{after removal}} - \text{Score}_{\text{before removal}}$. Groups were compared using a Wilcoxon signed rank test (continuous data). Results with $P<0.05$ (two-sided test) were regarded statistically significant.

Results

Patient, fracture, and treatment characteristics

Of the initial 250 patients, 162 patients healed uneventfully after internal fixation and were included. The remaining 88 patients were excluded, mainly since they had an arthroplasty as salvage procedure (N=69) or during primary surgery (N=16; Figure 2).

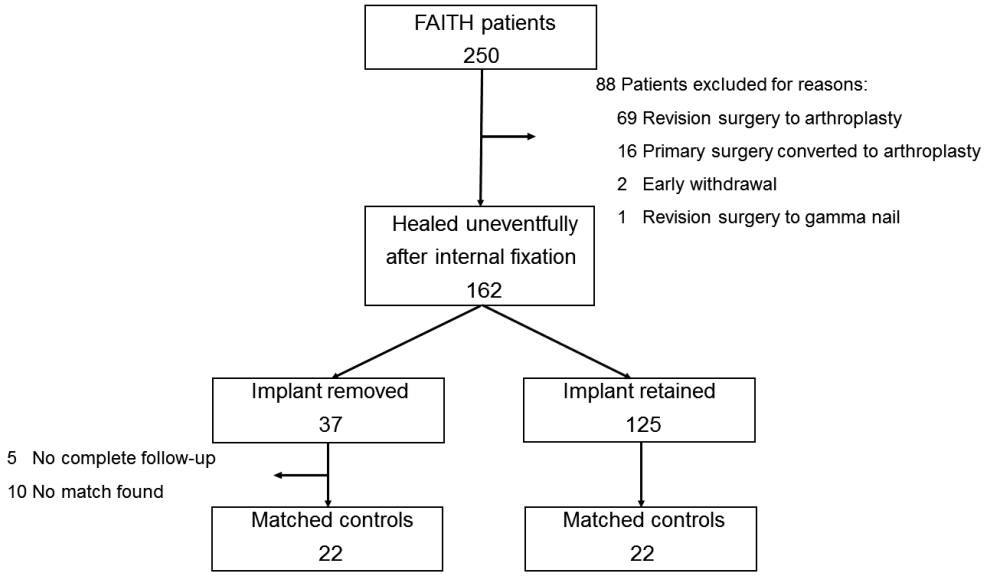

Figure 2. Flowchart of patients participating in this study

Patient, fracture, and treatment characteristics are shown in Table 1. Of the 162 patients who healed after internal fixation 37 patients had their implant removed (23%), at a median of 15 months after initial fracture surgery. Eight patients had an implant removal associated adverse event (22%); four patients sustained a bleeding or hematoma (11%), two patients a trochanteric bursitis (5%), one patient a urinary retention (3%), and one patient a wound infection (3%).

Patients who had their implant removed were significantly younger than patients who did not (median age 67 versus 72 years, P=0.024) and significantly more often independent ambulatory pre-fracture (100% versus 84% independently ambulatory, P=0.008). The implant removal patients also significantly more often had a Pauwels 3 type fracture (41% versus 22%, P=0.031) and an evident implant back-out on X-rays (54% versus 34%, P=0.035).

Table 1. Patient characteristics

	Crude analysis			Matched pair analysis		
	Implant removed (N=37)	**Implant retained (N=125)**	**P-value**	**Implant removed (N=22)**	**Implant retained (N=22)**	**P-value**
Age (years) [1*]	67 (60-73)	72 (62-79)	0.024	67 (61-74)	64 (60-72)	0.123
BMI (kg/m²)[1]	24 (21-26)	24 (22-26)	0.522	23 (20-26)	24 (21-28)	0.338
ASA >2[2*]	2 (5)	21 (17)	0.088	0 (0)	0 (0)	1.000
Female[2]	19 (51)	71 (57)	0.577	12 (55)	13 (59)	1.000
Displaced fracture (Garden III-IV)[2*]	18 (49)	38 (30)	0.050	11 (50)	11 (50)	1.000
Pauwels 3 fracture[2*]	15 (41)	27 (22)	0.032	6 (27)	6 (27)	1.000
Pre-fracture institutionalized[2*]	0 (0)	3 (2)	1.000	0 (0)	0 (0)	N.A.
Pre-fracture independent ambulatory[2*]	37 (100)	105 (84)	0.008	22 (100)	22 (100)	N.A.
Evident implant back-out[2]	20 (54)	41 (34)	0.035	11 (50)	2 (9)	0.004
Time to implant removal (months) [1]	15 (13-17)	N.A.	N.A.	15 (13-17)	N.A.	N.A.

BMI, Body Mass Index; ASA, American Society of Anesthesiologists.
Differences between the groups were tested with the Mann Whitney U-test (crude analysis) or Wilcoxon signed rank test (matched pair analysis) for numeric variables, and the Chi-squared test (crude analysis) or McNemar's chi-squared test (matched pair analysis) for categorical variables.
[1] Data are presented as median with P_{25}-P_{75} given between brackets. [2] Data are presented as number with percentages.
[*] This parameter was used to match pairs.

Crude analysis of patient self-reported health-related and disease-specific quality of life (SF-12 and WOMAC)

At baseline (*i.e.,* pre-fracture) patients who had their implant removed had significantly higher SF-12 scores than patients who healed without implant removal (107 versus 102 points, P=0.038). Especially the physical component summary scores were higher (Supplemental Table 1). WOMAC scores were not significantly different at baseline (97 versus 95 points, P=0.101).

After two years the SF-12 and WOMAC scores had decreased in patients who had their implant removed as well as in the patients who did not (Table 2). Again, this was mostly apparent in the physical component and function scores (Table 2). However, there was no significant difference in change between the groups; median change in SF-12 score-3 versus -3 points (P=0.700) and WOMAC score-3 versus-4 points (P=0.427; Table 2).

Table 2. Changes in patient self-reported physical functioning after two years follow-up

	Implant removed (N=37)	**Implant retained (N=125)**	**P-value**
SF-12			
Change Score 2 years	-3 (-19-4)	-3 (-14-2)	0.700
Change Physical (PCS) 2 years	-6 (-19--1)	-3 (-13-1)	0.167
Change Mental (MCS) 2 years	3 (-4-9)	1 (-4-6)	0.368
WOMAC			
Change Score 2 years	-3 (-32-0)	-4 (-18-1)	0.427
Change Pain 2 years	-5 (-33-0)	0 (-10-0)	0.156
Change Stiffness 2 years	0 (-38-0)	0 (-25-13)	0.086
Change Function 2 years	-4 (-35-0)	-5 (-19-0)	0.676

SF-12, Short Form 12; WOMAC, Western Ontario McMaster Osteoarthritis Index; PCS, Physical Component Summary; MCS, Mental Component Summary.
Scores were measured at baseline (*i.e.,* pre-fracture) and at two years later. These scores are presented in Supplemental table 1. The change in scores between these two moments was calculated using the formula: Change Score = Score $_{2\ years}$ – Score $_{baseline}$.
Data are presented as median with P_{25}-P_{75} given between brackets. Differences between the groups were tested with the Mann Whitney U-test.

Matched pair analysis

Of the 37 implant removal patients, five patients could not be included in the matched pair analysis because they did not have complete follow-up data. A match could be found for 22 of the remaining patients (Figure 2). The matched pairs had similar characteristics, as expected (Table 1). The only difference was a higher percentage of patients with evident implant back-out in the implant removal group (50% versus 9%, P=0.004).

At the follow-up moment directly before the implant removal (*i.e.,* mostly 12 or 18 months after initial fracture surgery), the implant removal patients reported significantly lower physical functioning scores than the patients who had their implant retained. This is

reflected in the SF-12 physical component summary score (44 versus 53 points, P=0.005) and all WOMAC sub-scores (pain 83 versus 100 points, P=0.001; stiffness 75 versus 100 points, P=0.010; function 82 versus 98 points, P=0.002; Table 3). At the follow-up moment directly after the implant removal (*i.e.,* mostly 18 or 24 months after initial fracture surgery), only a significantly lower WOMAC pain sub-score in the implant removal group remained (90 versus 98 points, P=0.036). Despite the second surgery and rehabilitation period, the implant removal patients still had an improvement of their physical functioning scores in the period of their implant removal, whereas the control group had not. This is reflected in an improvement in SF-12 physical component summary score (2 versus -4 points, P=0.024), WOMAC function sub-score (10 versus 0 points, P=0.030) and WOMAC total score (9 versus 0 points, P=0.019; Table 3).

Table 3. Effect of implant removal on patient self-reported physical functioning

	Implant removed (N=22)	**Implant retained (N=22)**	**P-value**
SF-12			
Score before removal	99 (87-109)	107 (98-110)	0.062
Physical (PCS) before removal	44 (35-49)	53 (46-56)	0.005
Mental (MCS) before removal	57 (48-62)	53 (50-61)	0.910
Score after removal	104 (92-109)	107 (98-109)	0.236
Physical (PCS) after removal	48 (42-51)	49 (43-52)	0.548
Mental (MCS) after removal	56 (48-61)	59 (56-62)	0.050
Change Score	0 (-4-10)	0 (-2-4)	0.485
Change Physical (PCS)	2 (-4-14)	-4 (-7-0)	0.024
Change Mental (MCS)	0 (-6-4)	4 (0-6)	0.168
WOMAC			
Score before removal	82 (62-88)	98 (88-100)	0.001
Pain before removal	83 (69-90)	100 (95-100)	0.001
Stiffness before removal	75 (50-91)	100 (75-100)	0.010
Function before removal	82 (61-88)	98 (89-100)	0.002
Score after removal	90 (74-98)	93 (87-100)	0.106
Pain after removal	90 (69-100)	98 (90-100)	0.036
Stiffness after removal	81 (75-100)	94 (88-100)	0.057
Function after removal	91 (71-100)	95 (85-100)	0.145
Change Score	9 (-2-16)	0 (-7-2)	0.019
Change Pain	5 (-1-11)	0 (-1-1)	0.051
Change Stiffness	6 (-3-38)	0 (-13-3)	0.176
Change Function	10 (-2-18)	0 (-6-3)	0.030

SF-12, Short Form 12; WOMAC, Western Ontario McMaster Osteoarthritis Index; PCS, Physical Component Summary; MCS, Mental Component Summary.
Scores were measured at the follow-up moment immediately before implant removal (mostly 12 or 18 months after initial fracture surgery) and after removal (mostly 18 or 24 months after initial fracture surgery). For the matched control the same follow-up moment was used. The change in scores between these two moments was calculated using the formula: Change Score = $\text{Score}_{\text{after removal}} - \text{Score}_{\text{before removal}}$. Data are presented as median with P_{25}-P_{75} given between brackets. Differences between the groups were tested with the Wilcoxon signed rank test.

Discussion

Implant removal after internal fixation of a femoral neck fracture had a significantly positive effect on patient functioning. The functional outcome scores of both the SF-12 and the WOMAC improved significantly more in the patients who had their implant removed than in the patients who did not, in a similar time period. Even though the implant removal patients were significantly more impaired than the control group before implant removal, they had similar general health-related and disease-specific quality of life after two years follow-up, which could be related to the implant removal. This positive effect of implant removal is confirmed in other studies on implant removal for different fractures.[9,10] The positive effect of implant removal may in fact even have been underestimated, as quality of life measurements were sometimes performed shortly after the implant removal surgery (*i.e.,* <6 months). Patients could therefore still have been rehabilitating from the second surgery at the time of follow-up. This may also explain why the WOMAC pain sub-scores were not significantly different between the groups after implant removal, although P-values approximated the 0.05 significance threshold.

The current study again emphasizes that disease-specific quality of life scores (*e.g.,* WOMAC) seem more appropriate in hip fracture patients than general health-related quality of life scores (*e.g.,* SF-12). The problem in the hip fracture population is a complex assortment of issues ranging from baseline health and frailty, social isolation and support, mental status and joint function and pain, which are all expressed in general health-related quality of life. The change in physical functioning through time was better expressed in the WOMAC total and sub-scores, than in the SF-12 total and sub-scores (Table 3).

Patients who had their implant removed after internal fixation of a femoral neck fracture were significantly younger and more often independent ambulatory pre-fracture than patients who did not. They also reported a better pre-fracture general health-related quality of life. This suggests that these patients were probably more mobile and active, and were therefore more impaired by the implant. Generally, it is likely that this patient category strived for a better outcome and performance level, and were less put off by the idea of a second surgery and rehabilitation period. In a previous study on implant removal after femur fractures, age also influenced the likelihood of removal.[6]

As expected, implant back-out was observed more often in patients who had their implant removed. Weight bearing can cause impaction at the fracture site and may result in femoral neck shortening, causing the implant to back-out.[1] The implant is then interfering with the surrounding soft tissues (*i.e.,* abductor muscles and fascia lata). This can result in pain and functional impairment, causing patients to have their implant removed. Apparently, implant back-out does not always cause complaints severe enough to decide on implant removal, as 34% of patients in the control group retained their implant despite an evident implant back-

out. In 46% of patients, on the other hand, the implant was removed without signs of an evident implant back-out. Implant back-out is therefore not always the cause of complaints. Implant removal patients more often had a Pauwels 3 type fracture. A previous study already indicated a Pauwels 3 type fracture as risk factor for femoral neck shortening and therefore causing increased implant back-out.[1]

The reason for implant removal was pain and/or functional impairment in all patients. It was therefore expected that SF-12 and WOMAC scores before implant removal were significantly worse in the implant removal patients, as shown in the results.

Implant removal seems a safe procedure with minimal risk. None of the adverse events that occurred were severe or caused permanent disability. The argument of extra costs seems refutable in this population, as a previously published cost analysis of this study group indicated that the implant removal patients were actually less expensive than the patients who healed without removal (€10,066 versus €17,405 after two years follow-up).[14] However, a selection bias may have played a role.

The main limitation of this study is the relatively low number of patients included, mainly in the matched pair analysis. If the study would be repeated with a higher number of patients and a longer period of follow-up after implant removal, it is likely that the positive effect of implant removal will even be more obvious. However, this is still the first study providing evidence on this topic, and significant effects are seen, even in this relatively small population. It would also be interesting to measure the effect on physical functioning using more objective parameters, such as gait parameters or muscle strength.[1] Unfortunately, our results can only prove a positive effect of implant removal for the patients who were selected in this study based on their symptoms and general condition. These patients were relatively young, healthy and independent pre-fracture. Results should therefore not be generalized.

In conclusion, implant removal after internal fixation of a femoral neck fracture had a significantly positive effect on patient functioning in this study. Patients who had their implant removed were younger, more often independently ambulatory pre-fracture, had a Pauwels 3 type fracture, and an evident implant back-out than patients who did not. Given the positive effects on patient functioning in this study, we suggest that implant removal should be considered more liberally in these patients, if there are persistent complaints of pain or unsatisfactory functional recovery after internal fixation of a femoral neck fracture.

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Supplemental Table 1. Patient self-reported physical functioning at baseline and after 2 years follow-up

	Total group / Crude analysis			Matched pair analysis		
	Implant removed (N=37)	Implant retained (N=125)	P-value	Implant removed (N=22)	Implant retained (N=22)	P-value
SF-12						
Score baseline	107 (99-114)	102 (92-110)	0.038	109 (100-114)	111 (100-114)	0.958
Physical (PCS) baseline	54 (48-57)	51 (43-55)	0.014	55 (49-58)	54 (51-56)	0.741
Mental (MCS) baseline	54 (48-59)	55 (48-59)	0.997	56 (51-59)	54 (47-61)	0.715
Score 2 years	106 (87-112)	98 (84-108)	0.219	106 (85-111)	107 (97-113)	0.099
Physical (PCS) 2 years	48 (36-52)	44 (33-52)	0.563	47 (37-52)	52 (43-57)	0.046
Mental (MCS) 2 years	58 (47-62)	55 (48-61)	0.296	58 (44-62)	55 (54-62)	0.375
Change Score	-3 (-19-4)	-3 (-14-2)	0.700	-5 (-19-2)	-3 (-12-5)	0.149
Change Physical (PCS)	-6 (-19--1)	-3 (-13-1)	0.167	-6 (-16--1)	-2 (-12-2)	0.170
Change Physical (MCS)	3 (-4-9)	1 (-4-6)	0.368	3 (-8-6)	1 (-2-8)	0.274
WOMAC						
Score baseline	97 (93-100)	95 (83-99)	0.101	98 (96-100)	98 (98-100)	0.063
Pain baseline	100 (93-100)	100 (90-100)	0.838	100 (100-100)	100 (100-100)	0.276
Stiffness baseline	100 (88-100)	88 (75-100)	0.091	100 (88-100)	100 (88-100)	0.593
Function baseline	99 (93-100)	95 (81-100)	0.047	99 (96-100)	99 (98-100)	0.157
Score 2 years	91 (65-96)	90 (72-97)	0.889	91 (65-96)	100 (91-100)	0.009
Pain 2 years	95 (65-100)	95 (85-100)	0.189	95 (65-100)	100 (99-100)	0.009
Stiffness 2 years	75 (56-100)	81 (63-100)	0.601	75 (50-100)	100 (88-100)	0.015
Function 2 years	94 (65-98)	90 (67-97)	0.583	94 (65-97)	100 (91-100)	0.024
Change Score	-3 (-32-0)	-4 (-18-1)	0.427	-5 (-35--2)	0 (-5-2)	0.009
Change Pain	-5 (-33-0)	0 (-10-0)	0.156	-5 (-35-0)	0 (0-0)	0.034
Change Stiffness	0 (-38-0)	0 (-25-13)	0.086	-13 (-38-0)	0 (-13-13)	0.012
Change Function	-4 (-35-0)	-5 (-19-0)	0.676	-6 (-35--1)	0 (-5-1)	0.023

SF-12, Short Form 12; WOMAC, Western Ontario McMaster Osteoarthritis Index; PCS, Physical Component Score; MCS, Mental Component Score.
Scores were measured at baseline (*i.e.,* pre-fracture) and after 2 years follow-up. The change in scores between these two moments was calculated using the formula: Change Score = $\text{Score}_{\text{at 2 years}} - \text{Score}_{\text{at baseline}}$.
Data are presented as median with P_{25}-P_{75} between brackets. Differences between the groups were tested with the Mann Whitney U-test (total group) or Wilcoxon signed rank test (matched pair analysis)

Chapter 10

Physical therapy after discharge following internal fixation of femoral neck fractures: characteristics of treatment

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Submitted

Abstract

Introduction: This study aimed to identify the characteristics of the physical therapy that femoral neck fracture patients treated with internal fixation receive after hospital discharge. Patients who had a shorter and longer period of therapy were compared (*i.e.*, <6 months versus ≥6 months) in order to define which patients may need a longer period of therapy.

Patients and methods: A cohort study was performed using a Dutch sample of a multicenter randomized controlled trial. Femoral neck fracture patients treated with internal fixation were included if they had had at least four therapy sessions during the first post-operative year. The attending physical therapists were asked to complete a questionnaire on the therapy that their patient received.

Results: One hundred-and-eight patients were included (median age 69 years). They received a median of 27 therapy sessions during 20 weeks. Functional exercise and active movement were the main training methods. At therapy start the long treatment group had significantly more restricted range of motion of the hip and significantly less abduction and extension strength than the short treatment group. The long treatment group was more restrained by anxiety.

Conclusions: The physical therapy that patients receive generally consists of active movement and functional exercise for less than two times a week, during 20 weeks. Hip range of motion and muscle strength at therapy start may predict the therapy duration. Restrictions caused by anxiety could also play a role. The additional therapy that the patients in the long treatment group received, adequately supported them to recover.

Introduction

Hip fractures are associated with 30% mortality at one year and a profound impairment of independence and quality of life.[1] Up to 50% of hip fracture patients do not rehabilitate to their pre-fracture ambulatory or functional status.[2,3] Poor recovery after a hip fracture is associated with an increased risk of future falls and fractures.[4,5] Risk factors of falls include decreased mobility, lower limb strength, and balance. Physical therapy after a hip fracture is aimed at improving these factors and regaining independence in functioning and activities of daily living.

Authors of national hip fracture guidelines and Cochrane reviews agree that early mobilization after hip fracture surgery (*i.e.*, within 48 hours), weight bearing as tolerated, and the use of multidisciplinary rehabilitation models are recommended.[6-12] However, recommendations on the characteristics (*i.e.,* intensity and structure) of the physical therapy that should be provided are not available, as evidence is inconclusive.

Studies on physical therapy after hip fracture treatment have shown varying results of the effect of an intensified rehabilitation program versus standard care.[5,8,13-15] These studies however, varied in the interventions studied (*i.e.,* location, intensity, and duration of the therapy, as well as moment of intervention start). Only one recent meta-analysis showed a significant impact of extended exercise rehabilitation programs on various functional abilities.[16] As benefits of an extended physical therapy program may exist, it would be interesting to identify a subgroup of patients that could benefit more from such a program. Despite these studies, it is not well described how physical therapists currently treat femoral neck fracture patients in daily practice.

The aim of this study was therefore to provide a detailed description of the characteristics of the physical therapy that femoral neck fracture patients treated with internal fixation currently receive after hospital discharge. In order to identify a subgroup of patients that could benefit from extended physical therapy, characteristics of patients who had a shorter and longer period of therapy were compared (*i.e.*, less than six months versus six months or longer).

Patients and Methods

This study was a cohort study using the Dutch sample of an international randomized controlled trial, the FAITH trial (Fixation using Alternative Implants for the Treatment of Hip fractures, NCT00761813), concerning femoral neck fracture patients treated with internal fixation. The study was approved by the local medical ethics committee.

Patients

In the Netherlands 14 hospitals participated in the FAITH trial and enrolled 250 patients between February 2008 and August 2009. Patients were included in the FAITH trial if they presented with a femoral neck fracture that required internal fixation. Patients were adults aged 50 years or older, not cognitively impaired, and ambulatory with or without a walking aid pre-fracture.[17] Surgical treatment consisted of multiple cancellous screws or a sliding hip screw. Early post-operative mobilization was encouraged, with weight bearing as tolerated. All patients received physical therapy during hospitalization. The in-hospital therapy was not standardized. Physical therapy after discharge (seven days post-surgery on average) was assigned based upon standard practice at the participating hospitals.[17] Consequently, out of hospital therapy started immediately after discharge for most patients; however, a part of the patients started therapy only several months after surgery.

All patients who received out-of-hospital physical therapy in the first post-operative year were included in this study. In an attempt to reduce confounding factors, patients who did not receive a significant period of physical therapy were excluded (*i.e.,* less than four therapy sessions after discharge or mortality within four weeks after surgery). Patients who underwent salvage arthroplasty within four weeks after the primary operation were also excluded, as their early implant failure probably significantly influenced rehabilitation. Finally, patients were excluded if no contact information of the attending physical therapist was available.

Measurements

The physical therapists of the included patients were retrospectively requested to complete a questionnaire on the therapy that their patient received. Physical therapists of both community-based programs and home-based programs were contacted. Six patients received therapy from two independent physical therapists. Data from both therapists were included.

The questionnaire was designed in collaboration with a regional panel of experienced therapists. The questionnaire included: (1) Total physical therapy duration; (2) Number of therapy sessions; (3) Frequency and duration of therapy sessions; (4) Therapy structure, divided into categories (*i.e.,* unsupervised practice at home, massage, passive and active movement, functional exercise, strength exercise/progressive resistant training); (5) Therapy goals and restrictions (*e.g.,* pain or anxiety); (6) Hip range of motion (ROM) and muscle strength (abductor and extensor strength were documented using the Medical Research Council (MRC) scale, as these muscle groups are generally considered most important for ambulation); (7) Use of walking aid; (8) Walking distance; (9) Domestic situation. Patients were asked to grade their physical therapist from zero to ten, indicating their satisfaction with the therapy they had received.

Data were divided into three time periods, 2 months, 6 months, and 12 months postoperatively. Data were collected from the first therapy session until either: (a) the last

therapy session; (b) one year post-surgery; (c) the date of a revision surgery (if applicable). A revision surgery was defined as a salvage arthroplasty (*e.g.,* due to avascular necrosis, non-union, or implant break-out).

Patients who received a short period of physical therapy were compared with patients who needed a longer period of therapy. Six months was chosen as a boundary based on previous studies.[5,8,13] Patients who underwent revision surgery within six months after the final therapy session were not included in the subgroup analyses, because the reason for the revision surgery and the resulting pain and disability were expected to confound the rehabilitation process.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (IBM Corp. Released 2011; IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY). Patient characteristics and physical therapy elements were described. Continuous variables are presented as medians with first and third quartile, categorical variables as numbers and percentage. Subgroup analyses were performed comparing patients who had a shorter and longer period of therapy. Numerical data were compared using a Mann-Whitney U-test. Categorical data were compared using a Chi-squared test. A P-value < 0.05 was taken as threshold of statistical significance.

Results

Demographic description of patients

Of the initial group of 250 patients, 88 patients had to be excluded following the exclusion criteria, as summarized in Figure 1. The attending physical therapists of the remaining 162 patients were contacted and 108 participated. The study population consisted of relatively young and healthy femoral neck fracture patients, with a median age of 69 years. Only 8% had severe comorbidities (ASA score >2; American Society of Anesthaesiologists classification). Prior to the fracture none of the patients were institutionalized and 8% used a walking aid (Table 1).

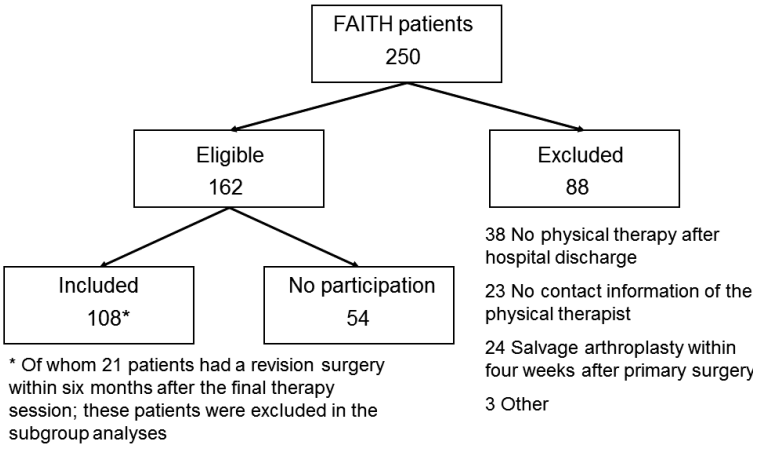

Figure 1. Flowchart of patients participating in the study

Table 1. Patient characteristics

	Total group (N=108)	**PT < 6 months* (N=52)**	**PT ≥ 6 months* (N=35)**
Age[1] (years)	69 (61-77)	68 (61–78)	69 (60-77)
Gender[2] (female)	60 (56)	30 (58)	15 (43)
Pre-fracture living status[2] (not institutionalized)	108 (100)	52 (100)	35 (100)
Pre-fracture mobility[2] (independent ambulator)	101 (94)	49 (94)	33 (94)
ASA-score[2] (ASA>2)	9 (8)	6 (12)	2 (6)

ASA, American Society of Anesthesiologists classification; PT, Physical therapy
* Patients who underwent a revision surgery within six months after the final therapy session were not included in these subgroup analyses.
[1] Data are presented as median with P_{25}-P_{75} given between brackets.
[2] Data are presented as number with percentages.

Intensity and structure of the physical therapy

The physical therapy that femoral neck fracture patients received after hospital discharge consisted of median 27 treatment session (P_{25}-P_{75} 16-41; Table 2). The median duration of the therapy was 20 weeks (P_{25}-P_{75} 10-38) and therapy started median 10 days (P_{25}-P_{75} 7-18) post-surgery. At two months 92% of patients received physical therapy, at six months 72%, and at twelve months 33%. At two months post-surgery 15% of patients received mainly therapy at a nursing home (*e.g.,* in-patient), 38% at a physical therapy clinic, and 47% at home (Table 2). In time, this shifted toward less in-patient therapy and less therapy at home. At twelve months 92% of patients were mainly treated at a physical therapy clinic. At all time periods >80% of patients received therapy less than three times per week. In 41-44% of patients the therapy session lasted less than 30 minutes (Table 2).

The structure of the therapy changed over time. At two months it consisted mainly of functional exercise (median 40% of the treatment (P_{25}-P_{75} 20-50%)), unsupervised practice at home (median 20% of the treatment (P_{25}-P_{75} 0-40%)), and active movement supervised by the physical therapist (median 20% of the treatment (P_{25}-P_{75} 10-30%); Table 2). During the first post-operative year this shifted towards less unsupervised practice at home and less active movement therapy (Figure 2). Instead, at twelve months the therapy consisted mainly of strength exercise (median 50% of the treatment (P_{25}-P_{75} 23-75%)) and functional exercise (median 20% of the treatment (P_{25}-P_{75} 0-43%); Table 2). In general, patients were satisfied with the physical therapy they had received and graded their therapist an eight (out of ten; P_{25}-P_{75} 7-9).

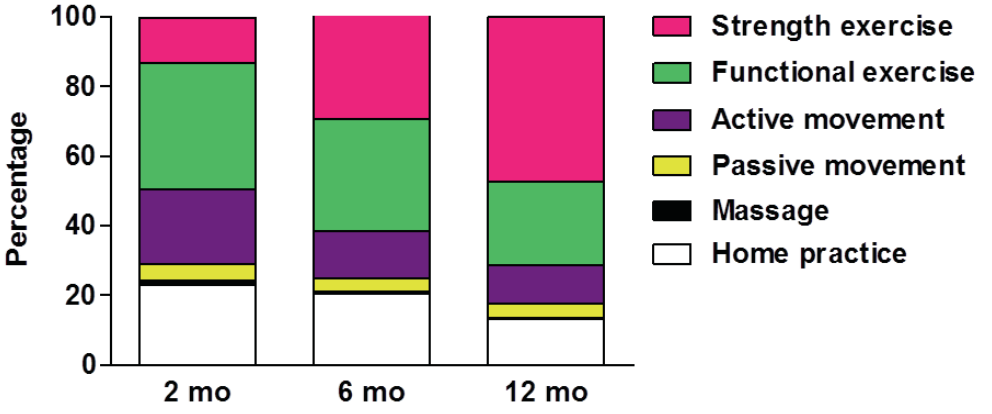

Figure 2. Part of the therapy spent on therapy subtypes (in percentage of the time spent).
Data are presented for three time periods: at two months, six months, and twelve months post-surgery.

Table 2. Intensity and structure of the physical therapy

	Total group (N=108)	PT <6 months (N=52)	PT ≥6 months (N=35)	P-value
Total number of therapy sessions[1]	27 (16-41)	20 (12-28)	52 (33-66)	<0.001
Time between surgery and physical therapy start (days)[1]	10 (7-18)	11 (7-22)	12 (7-22)	0.903
Total duration of physical therapy (weeks)[1]	20 (10-38)	14 (7-19)	46 (34-50)	<0.001
Main location of physical therapy[2]				
At 2 months[A]				
In-patient[†]	15 (15)	11 (23)	1 (3)	0.038
Out-patient, at clinic[††]	38 (38)	18 (38)	13 (41)	
Out-patient, at home[†††]	46 (47)[a]	18 (38)[a]	18 (56)[a]	
At 6 months[B]				
In-patient[†]	5 (6)	4 (13)	0 (0)	0.096
Out-patient, at clinic[††]	62 (80)	24 (77)	30 (88)	
Out-patient, at home[†††]	11 (14)[a]	3 (10)[a]	4 (12)[a]	
At 12 months[C]				
In-patient[†]	0 (0)	0 (0)	0 (0)	1.000
Out-patient, at clinic[††]	33 (92)	5 (100)	25 (89)	
Out-patient, at home[†††]	3 (8)[a]	0 (0)[a]	3 (11)[a]	
Frequency of therapy sessions[2]				
At 2 months[A] <3 times per week	82 (83)[a]	37 (79)[a]	29 (91)[a]	0.222
At 6 months[B] <3 times per week	76 (97)[a]	30 (97)[a]	34 (100)[a]	0.477
At 12 months[C] <3 times per week	36 (100)[a]	5 (100)[a]	28 (100)[a]	N.A.
Mean duration of therapy sessions[2]				
At 2 months[A] <30 minutes	43 (43)[a]	21 (45)[a]	15 (47)[a]	1.000
At 6 months[B] <30 minutes	32 (41)[a]	13 (42)[a]	14 (41)[a]	1.000
At 12 months[C] <30 minutes	16 (44)[a]	2 (40)[a]	14 (50)[a]	1.000
Part of therapy spent on therapy subtypes (%)[1]				
At 2 months[A]				
Unsupervised practice at home	20 (0-40)	20 (0-40)	15 (0-30)	0.480
Active movement[§]	20 (10-30)	20 (2-30)	25 (18-35)	0.027
Functional exercise[§§]	40 (20-50)[b]	40 (28-50)[a]	25 (20-50)[b]	0.049
At 6 months[B]				
Unsupervised practice at home	13 (0-30)	20 (3-38)	10 (0-25)	0.066
Functional exercise[§§]	30 (10-50)	30 (21-50)	30 (10-50)	0.311
Strength exercise[§§§]	25 (0-50)[b]	20 (0-48)[b]	50 (10-60)[c]	0.049
At 12 months[C]				
Unsupervised practice at home	0 (0-20)	10 (0-48)	0 (0-20)	0.553
Functional exercise[§§]	20 (0-43)	35 (0-81)	10 (0-39)	0.328
Strength exercise[§§§]	50 (23-75)[a]	10 (0-44)[a]	50 (33-79)[c]	0.063

PT, Physical therapy; N.A., Not applicable

Differences between the two groups were tested with the Mann-Whitney U-test for continuous variables, and with the Chi-squared test for categorical variables. Patients who underwent a revision surgery within six months after the final therapy session were not included in the subgroup analyses.

[1] Data are presented as median with P_{25}-P_{75} given between brackets. [2] Data are presented as number with percentages.

[A] At 2 months 9 patients did not receive physical therapy in the total group, 5 patients in the PT <6 months group, and 3 in the PT ≥6 months group. [B] At 6 months 30 patients did not receive physical therapy in the total group, 21 patients in the PT <6 months group, and 2 in the PT ≥6 months group. [C] At 12 months 72 patients did not receive physical therapy in the total group, 46 patients in the PT <6 months group, and 7 in the PT ≥6 months group.
[a] <5% Missing data. [b] 5-10% Missing data. [c] 10-15% Missing data.
[†] Physical therapy while rehabilitating in a skilled nursing facility. [††] Physical therapy in a physical therapy clinic. [†††] Physical therapy at home, supervised by a physical therapist.
[§] Active hip movement under supervision of a physical therapist. [§§] Functional exercises (*e.g.* transfers, stair climbing). [§§§] Strength exercises (*e.g.* progressive resistant training).

Short period of physical therapy (<6 months) versus a longer period (≥6 months)

Patient characteristics did not differ between the long and short treatment group at baseline, nor at therapy start (Table 1 and 3). At therapy start, patients in the long and short treatment groups did not have significantly different treatment goals (*i.e.,* 63% versus 49% independent ambulatory outdoor; (P=0.264), and 56% versus 36% unlimited walking distance (*i.e.,* >1 km; P=0.079)).

At therapy start, patients in the long treatment group had a significantly more impaired range of motion of the hip than patients in the short treatment group (Table 3). Hip flexion was significantly more restricted in the long treatment group (46% versus 18% very restricted (*i.e.,* <60°); P=0.018), as well as hip extension (53% versus 26% very restricted (*i.e.,* <0°); P=0.040), external rotation of the hip (33% versus 13% very restricted (*i.e.,* <0°); P=0.020), and internal rotation of the hip (50% versus 22% very restricted (*i.e.,* <0°); P=0.030). Hip muscle strength was also significantly more impaired in the long treatment group at therapy start. Patients in the long treatment group had significantly less abductor strength (63% versus 22% MRC <3; P=0.003), as well as extensor strength (38% versus 13% MRC <3; P=0.012). At therapy end, none of the physical performance parameters (*i.e.,* mobility, maximum walking distance, living status, hip range of motion, and hip muscle strength) differed significantly between the treatment groups.

No significant differences were noted in the structure of the physical therapy at any of the time periods (Table 2).

Finally, therapy restrictions were considered. At therapy start the long treatment group suffered significantly more often from anxiety to fall than the short treatment group (74% versus 48% of patients; p=0.023). This difference had disappeared by the time the therapy had ended (23% versus 20%; P=0.780). The number of patients hindered by pain in their rehabilitation process did not differ significantly (75 versus 90% at therapy start; P=0.149, and 37 versus 39% at therapy end; P=1.000).

Table 3. Patient physical function at the start and end of the physical therapy

	Total Group (N=108)	PT <6 months (N=52)	PT ≥6 months (N=35)	P-value
Mobility; Independent ambulator[1]				
At therapy start	5 (5)[a]	3 (6)[a]	2 (6)[b]	0.836
At therapy end	50 (48)[a]	27 (53)[a]	18 (55)[b]	1.000
Maximum walking distance >1 km[2]				
At therapy end	54 (53)[b]	27 (54)[a]	23 (70)[b]	0.175
Living status; Not institutionalized[3]				
At therapy start	81 (76)[a]	37 (73)[a]	28 (82)[a]	0.434
At therapy end	97 (92)[a]	45 (88)[a]	34 (100)[a]	0.077
ROM hip- Flexion				
At therapy start				
Very restricted (<60°)	34 (33)	9 (18)	15 (46)	0.018
Restricted (60°-90°)	51 (50)	28 (57)	15 (46)	
Not restricted (90°-120°)	17 (17)[b]	12 (25)[b]	3 (9)[b]	
At therapy end				
Very restricted (<60°)	4 (4)	0 (0)	2 (6)	0.206
Restricted (60°-90°)	31 (30)	11 (22)	8 (24)	
Not restricted (90°-120°)	67 (66)[b]	38 (78)[b]	23 (70)[b]	
ROM hip- Extension				
At therapy start				
Very restricted (<0°)	39 (38)	13 (26)	17 (53)	0.040
Restricted (0°-20°)	50 (49)	27 (54)	12 (38)	
Not restricted (20°-40°)	13 (13)[b]	10 (20)[a]	3 (9)[b]	
At therapy end				
Very restricted (<0°)	10 (10)	3 (6)	2 (6)	0.897
Restricted (0°-20°)	46 (45)	20 (40)	15 (46)	
Not restricted (20°-40°)	47 (46)[a]	27 (54)[a]	16 (49)[b]	
ROM hip – External rotation				
At therapy start				
Very restricted (<0°)	24 (26)	6 (13)	10 (33)	0.020
Restricted (0°-20°)	54 (57)	27 (59)	18 (60)	
Not restricted (20°-40°)	16 (17)[c]	13 (28)[c]	2 (7)[c]	
At therapy end				
Very restricted (<0°)	7 (7)	2 (4)	1 (3)	0.940
Restricted (0°-20°)	44 (46)	19 (42)	13 (41)	
Not restricted (20°-40°)	44 (46)[c]	24 (53)[c]	18 (56)[b]	
ROM hip – Internal rotation				
At therapy start				
Very restricted (<0°)	35 (37)	10 (22)	15 (50)	0.030
Restricted (0°-20°)	49 (52)	28 (61)	13 (43)	
Not restricted (20°-40°)	10 (11)[c]	8 (17)[c]	2 (7)[c]	
At therapy end				
Very restricted (<0°)	13 (14)	4 (9)	3 (10)	0.443
Restricted (0°-20°)	47 (50)	20 (44)	18 (58)	
Not restricted (20°-40°)	34 (36)[c]	21 (47)[c]	10 (32)[c]	

Muscle strength hip- Abduction				
At therapy start				
MRC <3	43 (44)	10 (22)	20 (63)	0.003
MRC 3	39 (40)	26 (57)	7 (22)	
MRC 4	14 (14)	9 (20)	4 (13)	
MRC 5	2 (2)[b]	1 (2)[c]	1 (13)[b]	
At therapy end				
MRC <3	5 (5)	0 (0)	1 (3)	0.496
MRC 3	11 (11)	2 (4)	3 (9)	
MRC 4	41 (42)	19 (41)	13 (41)	
MRC 5	41 (42)[b]	25 (54)[c]	15 (47)[b]	
Muscle strength hip- Extension				
At therapy start				
MRC <3	26 (27)	6 (13)	12 (38)	0.012
MRC 3	46 (48)	22 (49)	17 (53)	
MRC 4	20 (21)	15 (33)	2 (6)	
MRC 5	3 (3)[c]	2 (4)[c]	1 (3)[b]	
At therapy end				
MRC <3	2 (2)	0 (0)	0 (0)	0.391
MRC 3	12 (13)	3 (7)	5 (16)	
MRC 4	34 (36)	13 (29)	10 (31)	
MRC 5	47 (50)[c]	29 (64)[c]	17 (53)[b]	

MRC, Medical Research Council scale for the measurement of muscle strength; PT, Physical therapy
Data are presented as number with percentages. Differences between the two groups were tested with the Chi-squared test.
[1] As opposed to using a walking aid. [2] As opposed to limited maximum walking distance (<1 km). [3] As opposed to institutionalized.
[a] <5% Missing data. [b] 5-10% Missing data. [c] 10-15% Missing data.

Discussion

The physical therapy that femoral neck fracture patients treated with internal fixation received after hospital discharge consisted of median 27 therapy sessions during 20 weeks. Sessions lasted less than 30 minutes in 41-44% of the patients. Shortly after hospital discharge therapy was usually provided at home or in a nursing home, whereas one year post-surgery therapy was mainly provided at a physical therapy clinic. In the first six months the physical therapy mainly consisted of functional exercise (*e.g.* transfers, stair climbing), unsupervised practice at home, and supervised active hip movement. After six months strength exercise (*e.g.* progressive resistant training) was more frequently used. In general, patients were satisfied with the physical therapy they had received, not influenced by the therapy duration.

A recent meta-analysis provided evidence for the positive effects of extended physical therapy.[16] The therapy regimes in this meta-analysis seem slightly more intensive than the average therapy provided in our study. In our study 60% of the patients received physical

therapy for less than six months. Some of these patients still had a restricted physical function at therapy end. Extended therapy may have additional value for these patients, as significant beneficial functional effects were seen even after several months in the meta-analysis.[16] However, extended therapy leads to increased costs. It should therefore be considered with caution. The burden of health care costs already threatens to exceed the financial resources available. The current cost of out-patient physical therapy after hip fracture surgery has been calculated to be 1,354 euro after one year.[17]

Therefore, we attempted to identify a subgroup of patients that could benefit from extended therapy and compared the characteristics of patients who received therapy during less than six months and more than six months. Patients in the long treatment group had a significantly more impaired hip range of motion and muscle strength at therapy start. These patients need a longer and/or more intensive physical therapy to rehabilitate. Hip range of motion and muscle strength are therefore excellent predictors for the intensity and duration of the therapy needed, and should be used by physical therapists at the intake to design a therapy plan. Physical therapists also indicated that patients in the long therapy group suffered significantly more often from anxiety of falling, which interfered with rehabilitation progress. It therefore seems important to notice fear of falling at an early stage, in order to focus therapy to reducing this fear. Characteristics as mobility, living status, and treatment goals did not differ significantly between the treatment groups and therefore do not seem useful predictors for the duration and intensity of the therapy required. At therapy end, the treatment groups had equal physical performance parameters, indicating that the additional therapy adequately supported the patients in the long treatment group to recover. Results should however not be extrapolated to all hip fracture patients, as the study group consisted of relatively young, healthy patients, in a western society.

The strength of our study is the sample size and in-depth description of the physical therapy provided. This has never previously been reported so extensively. Also, previous reports usually focused on either therapy at home, in a clinic, or in a rehabilitation facility, whereas in this study all treatment modalities were combined.[5,15,16] A limitation is the retrospective nature of the study causing an incomplete database. Thirty-six physical therapists declared incomplete documentation precluded their participation. Documentation should receive more attention, facilitated by a standard documentation tool that is yet to be developed. Selection bias seems unlikely, as the patient characteristics (*i.e.,* age, pre-fracture living status and mobility, and ASA score) of the 54 eligible patients who did not participate did not differ from the included population.

Remarkably, 38 patients (15%) did not receive therapy after discharge. This may be explained by short-term mortality (three patients) and salvage arthroplasty (four patients). Other reasons could be that these patients were either young (10 patients aged <65 years) and in a good condition, perhaps not needing therapy, or that they were older (15 patients

aged >75 years) and in a condition unable to rehabilitate (11% institutionalized pre-fracture, 26% use of aids pre-fracture and 21% ASA 3).

In conclusion, the physical therapy that femoral neck fracture patients received after internal fixation is slightly less intensive than what is suggested in physical therapy literature. Extended therapy may have beneficial effects for selected patients. Hip range of motion and muscle strength at therapy start are predictors for therapy duration. Anxiety to fall may also play a role. These factors should be taken into account when designing a treatment plan and prescribing extended physical therapy. Evidence-based physical therapy should be incorporated into national hip fracture guidelines in order to stimulate uniform treatment.

Ethical approval: The study was approved by the local medical ethics committee at the Erasmus MC, University Medical Center Rotterdam.

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Chapter 11

Summary and conclusions (English)

This thesis consists of three parts. Part 1 described aspects of the organization of trauma related trials. Part 2 analyzed the uniformity of current femoral neck fracture treatment and adherence to the Dutch guideline on hip fracture treatment. The implications of treatment with internal fixation on health care costs were also described. Part 3 focused on aspects on functional outcome after internal fixation of a femoral neck fracture.

Part 1

In **Chapter 2** two different trial management strategies have been compared to analyze how they affected trial performance in a multicenter RCT. A centrally located and financed trial coordinator to manage all trial related tasks in the participating sites resulted in better trial progression and a similar follow-up, compared with tasks managed by local study coordinators who receive per patient payment. Central coordination resulted in both a shorter trial start-up period (by 191 days) and a higher inclusion rate (up to seven times). Central trial coordination is therefore advised when designing an orthopaedic trauma trial, provided that the hospitals are located within a manageable distance.

In **Chapter 3** an overview of the International Conference of Harmonization-Good Clinical Practice (ICH-GCP) guideline in the context of conducting an implant trial in orthopedic trauma surgery was provided. This guideline has been developed in order to assure that the rights, safety, and well-being of trial subjects (*i.e.,* patients) are protected. Aspects to consider when designing and conducting a trial are: (a) a detailed protocol, (b) obtaining ethics approval for the study, (c) registration of the trial in a public trial registry, (d) assuring adequate informed consent, (e) reporting adverse events and revision surgeries to the ethics committee and data safety and monitoring board, (f) involving a dedicated research team, and (g) ensure complete and high-quality data. When clinically evaluating a (new) medical device, the CE (Conformité Européenne; in English European Conformity) in Europe, or the FDA (Food and Drug Administration) in the US must give approval. These kind of regulatory trials are more complex and time-consuming, and require even stricter adherence to ICH-GCP rules. A clinical audit can be performed in order to ensure that trials are conducted in compliance with the trial protocol and all applicable guidelines and regulatory requirements.

Part 2

In **Chapter 4** we investigated the extent to which treatment of femoral neck fracture patients in the Netherlands corresponded with national guidelines. Data from 1,250 consecutive femoral neck fracture patients were collected retrospectively. These patients had been treated in 14 hospitals between February 2008 and August 2009. Of these patients 59% had been treated with arthroplasty, 39% with internal fixation, and 2% received a non-operative treatment. Whereas 74% of the treatments adhered to the guidelines, 12% did not. In 14% adherence could not be determined from the available data. Most deviations from the

guideline concerned treatment of elderly patients with a displaced fracture, as well as implant use in internal fixation. In order to study if patient characteristics may have played a role in treatment decision, according to guidelines, differences in patient characteristics between the treatment groups were determined. Arthroplasty was preferred over internal fixation in elderly patients with severe comorbidity, pre-fracture osteoporosis and in patients with a displaced fracture, who were ambulatory with aids pre-fracture (Odds Ratio, OR 2.2-58.1). Sliding hip screws were preferred over cancellous screws in displaced fractures (OR 1.9). We concluded that overall guideline adherence was good. In order to improve the guideline and reinforce an even more uniform treatment of femoral neck fracture patients additional data with a higher level of evidence are required. Evidence on the treatment of elderly patients with a displaced fracture as well as implant use in internal fixation is mainly required.

In **Chapter 5** the cumulative incidence of non-simultaneous bilateral femoral neck fractures was determined. In order to analyze if femoral neck fracture treatment is uniform, we quantified whether similar characteristics at the time of both fractures lead to similarity in treatment. From the previously available database of 1,250 consecutive femoral neck fracture patients, patients with a previous contralateral femoral neck fracture were identified by reviewing radiographs and patient files. Nine percent of the patients had sustained a non-simultaneous bilateral femoral neck fracture, with a median interval of 25 months between the two fractures. Overall, 73% of patients were treated similarly for both fractures in terms of non-operative treatment, internal fixation or arthroplasty. Treatment similarity was 88% in the 33 patients with identical Garden classification of both fractures. It therefore seems that trauma and orthopedic surgeons generally agree on the treatment of the different types of femoral neck fractures. However, diversity in the use of the specific type of arthroplasty (hemi- versus total arthroplasty) or implant (sliding hip screw versus cancellous screws) remained, even in the patients with identical Garden classification.

In **Chapter 6** a detailed overview of the costs and health care consumption of patients treated for a femoral neck fracture with internal fixation was provided. A prospective cohort study was performed alongside the Dutch sample of the FAITH trial (Fixation using Alternative Implants for the Treatment of Hip fractures). Patient characteristics and health care consumption were collected during a two year follow-up period. Hospital costs during primary stay and follow-up were calculated, as well as costs related to rehabilitation and changes in living situation. As the risk of revision surgery in internal fixation patients is considerable, costs were compared between non-revision surgery patients, implant removal patients, and revision arthroplasty patients. A total of 248 patients were included. Mean total costs per patient at two years follow-up were €19,425. In the non-revision surgery patients total costs were €17,405 (N=137), in the implant removal patients €10,066 (N=38), and in the revision arthroplasty patients €26,733 (N=67). The main determinant was the cost of admission to a rehabilitation center/nursing home. Other important contributing costs were

related to the primary surgery, admission days, physical therapy, and revision surgeries. As a result, costs were especially high in elderly with comorbidity, who were less independent pre-fracture, and have a longer admission to the hospital and/or a nursing home. Costs were also understandably higher in revision surgery patients. The low costs in implant removal patients are probably explained by patient selection, as these patients were younger, healthier, more independent and mobile pre-fracture. They therefore probably required less care and rehabilitation, generating less costs. The two years follow-up costs in our study were comparable to published costs in other Western societies (both Europe and USA).

Part 3

In **Chapter 7** long-term physical limitations in patients who healed after internal fixation of a femoral neck fracture were studied. Femoral neck shortening (leading to limb length shortening) was assessed as this is an important limitation that may arise after internal fixation. Implants allow fracture fragments to slide along the implant. This permits impaction at the fracture site, especially when subjected early to an axial loading force during weight bearing. Risk factors for femoral neck shortening were determined, as well as its consequences on gait pattern and muscle strength. Femoral neck shortening was measured on X-rays. Gait parameters were measured using plantar pressure measurement. Maximum isometric forces of the hip muscles were measured using handheld dynamometry. Differences between the fractured leg and the contralateral leg were calculated. Patients with little or no shortening (<0.75 cm), moderate shortening (0.75-1.50 cm), and severe shortening (>1.50 cm) were compared using univariate and multivariable analyses. Seventy-six patients were included from the Dutch sample of the FAITH trial. The median femoral neck shortening was 1.1 cm. Overall, subtle changes in gait pattern, a reduced gait velocity (median 1.1 m/s), and reduced abductor muscle strength (median -20 N) were observed. Patient self-reported functioning was good. Age, weight, and Pauwels classification were risk factors for femoral neck shortening. Femoral neck shortening decreased gait velocity and seemed to impair gait symmetry and physical functioning. In conclusion, internal fixation of femoral neck fractures resulted in permanent physical limitations. The relatively young and healthy patients in our study seemed capable of compensating. Attention should be paid to femoral neck shortening and proper correction with a heel lift, as inadequate correction may cause physical complaints and influence outcome.

In **Chapter 8**, in order to determine if outcome after salvage arthroplasty for failed internal fixation is satisfactory, functional outcome of these patients was studied. Outcome was compared with outcome of patients who healed uneventfully after internal fixation of a femoral neck fracture. In a secondary cohort study alongside the FAITH trial patient independency, health-related and disease-specific quality of life (SF-12 and WOMAC scores), as well as gait pattern and muscle strength were measured and compared. Similar methods

were used as described in Chapter 7. Of 248 internal fixation patients, salvage arthroplasty was performed in 68 patients (27%). Salvage arthroplasty patients had a significantly lower WOMAC score (median 73 versus 90, P=0.016) after two years follow-up than patients who healed uneventfully after internal fixation. Health-related quality of life (SF-12) and patient independency did not differ significantly between the groups. Gait analysis showed a significantly impaired progression of the center of pressure line in the salvage surgery patients (median ratio -8.9 versus 0.4, P=0.013), indicating an impaired transfer of load underneath the affected limb. This could be the effect of impaired balance, or impaired muscle strength. Indeed a significant greater loss of abduction strength was measured in the salvage arthroplasty patients (median -25.4 versus -20.4 N, P=0.025). We therefore concluded that salvage arthroplasty patients have inferior functional outcome than patients who primarily heal after internal fixation of a femoral neck fracture. However, despite lower functional outcome scores, these salvage arthroplasty patients do not have a worse health-related quality of life. This is probably explained by an adequate coping mechanism of the relatively young and healthy study population. The worse functional outcome after salvage arthroplasty suggests that patients receiving internal fixation of a femoral neck fracture should be selected carefully, in an attempt to avoid salvage surgery.

In **Chapter 9** the effect of implant removal after internal fixation of a femoral neck fracture on physical functioning was analyzed, as knowledge on this topic is limited. After healing of a femoral neck fracture the implant is sometimes removed because it can cause local irritation and functional impairment. This is caused by implant back-out as a result of impaction at the fracture site. It is however unknown which patients are well selected candidates for removal. Therefore, characteristics of patients who had their implant removed were studied in a secondary cohort study alongside the FAITH trial. Patient characteristics and quality of life (SF-12 and WOMAC scores) were compared between patients who had their implant removed and patients who did not. Matched pairs were selected based on patient/fracture characteristics and pre-fracture physical functioning. Of 162 healed internal fixation patients, 37 had their implant removed (23%). These patients were younger (median age 67 versus 72 years, P=0.024) and more often independently ambulatory pre-fracture (100% versus 84%, P=0.008) than patients who did not. They more often had evident implant back-out on X-rays (54% versus 34%, P=0.035), possibly related to a higher rate of Pauwels 3 fractures (41% versus 22%, P=0.032). In time, quality of life improved more in implant-removal patients (+2 versus-4 points SF-12 (physical component), P=0.024; +9 versus 0 points WOMAC, P=0.019). The positive effect of implant removal on quality of life (mainly disease-specific and function-related) indicates that implant removal should be considered liberally in patients after internal fixation if pain persists or functional recovery is unsatisfactory. This effect was seen in a study population of relatively young patients, who are independent ambulators pre-fracture and have an evident implant back-out on X-rays.

In **Chapter 10** the characteristics (*i.e.,* frequency, duration, and structure) of the physical therapy that femoral neck fracture patients treated with internal fixation received after hospital discharge were identified. Physical therapy after hip fracture surgery is important for regaining independent functioning. However, few reports described how physical therapists currently treat femoral neck fracture patients in daily practice. A recent meta-analysis showed slight benefits of an extended, intensified physical therapy program. In order to define which patients may need a longer period of therapy, the characteristics of patients who had a short period of therapy (*i.e.*, <6 months) and a longer period of therapy (*i.e.*, ≥6 months) were compared. In a cohort study alongside the FAITH trial all patients were included who had had a minimum of four therapy sessions during the first post-operative year. The attending physical therapists were asked to complete a questionnaire on the therapy that their patient received. The physical therapists of 108 patients responded. Patients received median 27 therapy sessions during 20 weeks. Functional exercise and active movement were the main training methods. This is slightly less intensive than what is advised in a recent physical therapy meta-analysis. At therapy start the long treatment group had significantly more restricted range of motion of the hip and significantly less abduction and extension strength than the short treatment group. The long treatment group was also more restrained by anxiety during the treatments. We concluded that hip range of motion and muscle strength at the start of the therapy are predictors for the duration of the physical therapy. Restrictions caused by anxiety to fall may also play a role. However, the additional therapy that the patients in the long treatment group received, adequately supported them to recover. Hip range of motion and muscle strength, as well as anxiety to fall, should be taken into account when designing a physical therapy treatment plan and deciding on prescribing extended physical therapy.

In summary, this thesis provides evidence that:

- A central, financed trial coordinator to manage all trial related tasks in participating sites is a recommended strategy to improve trial progression (Chapter 2)
- Adequate knowledge on the International Conference of Harmonization-Good Clinical Practice (ICH-GCP) guideline is important when conducting an implant trial in orthopedic trauma surgery (Chapter 3)
- The current treatment of femoral neck fracture patients is in agreement with the Dutch national guideline in at least 74% of patients (Chapter 4)
- The current treatment of non-simultaneous bilateral femoral neck fractures is uniform in 73-88% of patients (Chapter 5)
- In and out of hospital cost of internal fixation of femoral neck fracture patients is approximately €16,000 at one year follow-up and €19,000 at two years follow-up (Chapter 6)

- Internal fixation of femoral neck fracture patients leads to femoral neck shortening and secondary permanent physical limitations in a majority of patients (Chapter 7)
- Salvage arthroplasty patients have inferior functional outcome than patients who heal after internal fixation of a femoral neck fracture (Chapter 8)
- Implant removal positively influences function-related quality of life in patients after internal fixation with persisting pain or unsatisfactory functional recovery (Chapter 9)
- The physical therapy that femoral neck fracture patients receive after internal fixation generally consists of active movement, functional exercise, and independent practice for less than two times a week, during 20 weeks (Chapter 10)

In **Chapter 13** a general discussion of the main findings in this thesis and its consequences on treatment of patients with femoral neck fractures was provided, including future perspectives.

Chapter 12

Samenvatting en conclusies (Nederlands)

Dit proefschrift bestaat uit drie delen. Deel 1 beschrijft hoe gerandomiseerde studies (RCTs) verricht dienen te worden in trauma onderzoek. In Deel 2 is onderzocht of de huidige behandeling van patiënten met een collum femorisfractuur uniform is en in welke mate de nationale richtlijn gevolgd wordt. De gezondheidszorgkosten van patiënten bij wie een collum femorisfractuur met interne fixatie is behandeld zijn ook beschreven. Deel 3 beschrijft de functionele uitkomst van patiënten na interne fixatie van een collum femorisfractuur.

Deel 1

In **Hoofdstuk 2** is het effect onderzocht van twee verschillende managementstrategieën op de voortgang van een multicenter RCT. Een gefinancierde, centrale studiecoördinator voor alle studiegerelateerde taken in alle deelnemende centra is vergeleken met lokale onderzoekers/ studiecoördinatoren, die dezelfde taken verrichten en daarvoor een vergoeding per patiënt ontvangen. Centrale coördinatie resulteerde in betere studieprogressie en een vergelijkbare follow-up. Centrale studiecoördinatie resulteerde bovendien in een kortere opstartperiode van de studie (191 dagen) en een hoger inclusiepercentage (tot zeven keer). Daarom wordt centrale coördinatie geadviseerd bij het opzetten van een nieuwe studie in de orthopedische traumachirurgie, onder de voorwaarde dat de deelnemende ziekenhuizen zich binnen een bereisbare afstand bevinden.

In **Hoofdstuk 3** is een overzicht gegeven van de Conference of Harmonization-Good Clinical Practice (ICH-GCP) richtlijn in de context van de uitvoering van een implantaatstudie in de orthopedie of traumachirurgie. Deze richtlijn is ontworpen om de rechten, veiligheid en het welzijn van de deelnemende patiënten te beschermen. Met de volgende aspecten dient rekening gehouden te worden tijdens het opzetten en uitvoeren van een studie: (a) een gedetailleerd protocol, (b) verkrijgen van goedkeuring van een medisch ethische toetsingscommissie, (c) studieregistratie in een openbaar studieregister, (d) zorg dragen voor adequate 'informed consent', (e) rapportage van ernstige complicaties en revisieoperaties aan de medisch ethische toetsingscommissie en de 'data safety and monitoring board', (f) een toegewijd onderzoeksteam en (g) zorg dragen voor complete data van hoge kwaliteit. Voordat een (nieuw) implantaat klinisch geëvalueerd kan worden, moet dit implantaat goedgekeurd zijn door de CE (Conformité Européenne) in Europa of de FDA (Food and Drug Administration) in de US. Klinische studies met nieuwe implantaten zijn complexer en kosten meer tijd. Bovendien dienen ze nog strikter te voldoen aan ICH-GCP regels. Een klinische audit kan worden verricht om te controleren of een studie conform het studieprotocol is uitgevoerd en of alle relevante richtlijnen en wetgeving gevolgd zijn.

Deel 2

In **Hoofdstuk 4** is beschreven in welke mate de behandeling van collum femorisfracturen in Nederland conform de nationale richtlijn is. Gegevens van 1.250 opeenvolgende patiënten met een collum femorisfractuur werden retrospectief verzameld. Deze patiënten zijn in de periode februari 2008 tot en met augustus 2009 behandeld in 14 ziekenhuizen. Van deze patiënten werd 59% behandeld met een arthroplastiek, 39% met interne fixatie en 2% conservatief. Terwijl 74% van de behandelingen conform de richtlijn was, week 12% van de behandelingen van de richtlijn af. In 14% kon op basis van de beschikbare gegevens niet vastgesteld worden of de behandeling overeenkwam met de richtlijn. Er werd het meest afgeweken van de richtlijn in het geval van oudere patiënten met een gedisloceerde fractuur en bij de implantaatkeuze in het geval van interne fixatie. In de richtlijn wordt geadviseerd rekening te houden met de patiëntkarakteristieken tijdens de besluitvorming over de juiste behandeling. Om te kunnen vaststellen of patiëntkarakteristieken inderdaad een rol hebben gespeeld zijn patiëntkarakteristieken van de behandelgroepen vergeleken. Arthroplastiek werd geprefereerd boven interne fixatie voor patiënten met een gedisloceerde fractuur, hogere leeftijd, ernstigere comorbiditeit, osteoporose in de voorgeschiedenis, of pre-fractuur mobiliteit met een hulpmiddel (Odds Ratio, OR 2,2-58,1). Een dynamische heupschroef had de voorkeur boven gecannuleerde schroeven bij een gedisloceerde fractuur (OR 1,9). Wij concludeerden dat de richtlijnadherentie in het algemeen goed is. Het incorporeren van nieuw wetenschappelijk bewijs in een verbeterde versie van de richtlijn kan de adherentie verder vergroten en een nog meer uniforme behandeling van patiënten met een collum femorisfractuur bewerkstelligen. Een hoger level of evidence is hiervoor nodig, met name met betrekking tot de beste behandeling van ouderen met een gedisloceerde fractuur en implantaatkeuze in het geval van interne fixatie.

In **Hoofdstuk 5** is de cumulatieve incidentie van niet-simultane bilaterale collum femorisfracturen bepaald. Om te onderzoeken of de behandeling van collum femorisfracturen uniform is, werd bestudeerd of gelijke karakteristieken ten tijde van de beide fracturen ook resulteerden in gelijke behandeling. Uit een eerder beschikbare database met 1.250 patiënten met een collum femorisfractuur werden patiënten met een contralaterale collum femorisfractuur in de voorgeschiedenis geïdentificeerd. Dit werd gebaseerd op gegevens uit de medische status en tekenen van een eerdere fractuur op röntgenfoto's. Negen procent van de patiënten had een niet-simultane bilaterale collum femorisfractuur doorgemaakt, met een mediaan interval van 25 maanden tussen de fracturen. In 73% van deze patiënten waren beide fracturen gelijk behandeld als gekeken werd naar conservatieve behandeling versus interne fixatie en versus arthroplastiek. In de 33 patiënten met een identieke Garden classificatie van beide fracturen werden de fracturen zelfs gelijk behandeld in 88%. Traumachirurgen en orthopeden blijken derhalve in het algemeen overeen te stemmen in hun behandeling van de verschillende typen collum femorisfracturen. Echter, heterogeniteit in het type arthroplastiek

(hemi- versus totale heup arthroplastiek) en type implantaat (dynamische heupschroef versus gecannuleerde schroeven) was wel aanwezig, zelfs bij patiënten met een identieke Garden classificatie van de fractuur.

In **Hoofdstuk 6** is een gedetailleerd overzicht gegeven van de kosten en het zorggebruik van patiënten met een collum femorisfractuur behandeld met interne fixatie. Een prospectieve cohortstudie was verricht naast het Nederlandse deel van de FAITH studie (Fixation using Alternative Implants for the Treatment of Hip fractures). Patiëntkarakteristieken en zorggebruik werden verzameld tijdens een follow-up periode van twee jaar. Ziekenhuiskosten tijdens de initiële opname en tijdens follow-up werden berekend, evenals de kosten gerelateerd aan revalidatie en een veranderde woonsituatie. Vanwege het aanzienlijke risico op revisieoperaties bij patiënten na interne fixatie, werden kosten tussen drie subgroepen vergeleken: (1) patiënten die succesvol uitbehandeld zijn met het implantaat *in situ*, (2) patiënten bij wie het implantaat is ververwijderd na genezing en (3) patiënten die een revisiearthroplastiek hebben ondergaan. In totaal werden 248 patiënten geïncludeerd. De gemiddelde totale kosten per patiënt na twee jaar follow-up waren €19.425. In de groep patiënten die succesvol uitbehandeld werden met het implantaat *in situ* waren deze kosten €17.405 (N=137), in de patiënten bij wie het implantaat verwijderd is €10.066 (N=38), en in de patiënten die een revisiearthroplastiek ondergingen €26.733 (N=67; P<0,001). De kosten van verblijf in een revalidatiecentrum of verpleeghuis was de belangrijkste kostendeterminant. Andere belangrijke bijdragende factoren waren de kosten van de primaire operatie en ziekenhuisopname, fysiotherapie en revisieoperaties. Daarom waren de kosten met name hoog in oudere patiënten die pre-fractuur reeds comorbiditeit hadden en minder mobiel waren, mede omdat zij langdurig opgenomen waren in het ziekenhuis dan wel een verpleeghuis. Kosten waren ook hoger in patiënten die een revisiearthroplastiek ondergingen. De kosten na twee jaar follow-up in onze studie waren vergelijkbaar met de kosten gepubliceerd in andere Westerse landen (zowel Europa als de VS).

Deel 3

In **Hoofdstuk 7** zijn de langdurige fysieke beperkingen van patiënten na interne fixatie van een collum femorisfractuur bestudeerd. Collumverkorting (resulterend in een beenlengteverschil) werd gemeten, omdat dit een belangrijke beperking is die het gevolg kan zijn van interne fixatie. Dit ontstaat doordat fractuurfragmenten kunnen bewegen langs het implantaat. Hierdoor is impactie ter plaatse van de fractuur mogelijk. Dit gebeurt vooral na vroegtijdige blootstelling aan axiale krachten tijdens belasten. Risicofactoren voor collumverkorting en de consequenties van collumverkorting op looppatroon en spierkracht werden bepaald. Collumverkorting werd radiologisch gemeten. Looppatroonparameters werden gemeten door middel van voetdrukmetingen op een loopplank. Maximale isometrische spierkracht van de heupspieren werd gemeten met een dynamometer. Verschillen tussen het gebroken

been en de contralaterale zijde werden berekend. Uitkomsten van patiënten met weinig/geen collumverkorting (<0,75 cm), matige collumverkorting (0,75-1,50 cm) en ernstige collumverkorting (>1,50 cm) werden vergeleken door middel van univariate en multivariate analyses. Zesenzeventig patiënten werden geïncludeerd uit het Nederlandse deel van de FAITH studie. De mediane collumverkorting was 1,1 cm. Subtiele afwijkingen in de looppatroonparameters, een afgenomen loopsnelheid (mediaan 1,1 m/s) en een afgenomen spierkracht van de abductoren (mediaan -20 N) werden gemeten. Patiënten rapporteerden een goede functie. Leeftijd, gewicht en Pauwels classificatie bleken risicofactoren voor het ontstaan van collumverkorting. Collumverkorting had een negatief effect op loopsnelheid en leek ook de symmetrie in het looppatroon en het fysiek functioneren negatief te beïnvloeden. Concluderend resulteerde interne fixatie van een collum femorisfractuur in verscheidene permanente fysieke beperkingen. De relatief jonge en gezonde patiënten in onze studie leken in staat om te compenseren voor deze beperkingen. Chirurgen zouden aandacht moeten besteden aan collumverkorting en adequate correctie met een hak-/zoolaanpassing, gezien inadequate correctie fysieke klachten en beperkingen kan veroorzaken, en daarmee de uitkomst beïnvloedt.

In **Hoofdstuk 8** werd de functionele uitkomst onderzocht van patiënten die een revisiearthroplastiek ondergingen vanwege gefaalde interne fixatie van een collum femorisfractuur, om te bepalen of deze uitkomst acceptabel is. Een vergelijking werd gemaakt met patiënten die zijn genezen na interne fixatie. In een secundaire cohortstudie naast de FAITH studie werden woonsituatie, mobiliteit, algemene gezondheidsgerelateerde en ziektespecifieke kwaliteit van leven (QOL), looppatroon en spierkracht van deze patiënten gemeten en vergeleken. Vergelijkbare methoden werden gebruikt als beschreven in Hoofdstuk 7. Van de 248 deelnemende patiënten ondergingen 68 patiënten (27%) een revisiearthroplastiek. De revisiepatiënten hadden een significant lagere WOMAC score na twee jaar follow-up (mediaan 73 versus 90, P=0,019) dan de patiënten die zijn genezen na interne fixatie. De algemene gezondheidsgerelateerde QOL (SF-12), woonsituatie en mobiliteit waren niet significant verschillend tussen de groepen. Looppatroonanalyse toonde een significant verminderde progressie van de center-of-pressure lijn in de revisiepatiënten (mediane ratio -8,9 versus 0,4, P=0,013), passend bij een verminderde verplaatsing van druk onder het aangedane been. Dit kan het effect zijn van disbalans of minder spierkracht. Inderdaad werd een significant meer afgenomen spierkracht van de abductoren gemeten in de revisiepatiënten (mediaan -25,4 versus -20,4 N, P=0,025). Wij concludeerden daarom dat patiënten na een revisiearthroplastiek een slechtere functionele uitkomst hebben dan patiënten die genezen na interne fixatie van een collum femorisfractuur. Dit komt echter niet tot uiting in een slechtere woonsituatie, mobiliteit, of QOL van de patiënten. Dit komt waarschijnlijk door de adequate coping mechanismen van de relatief jonge en gezonde studiepopulatie. De slechtere functionele uitkomst na revisiearthroplastiek suggereert dat

patiënten met een collum femorisfractuur zorgvuldig geselecteerd moeten worden voor interne fixatie om een revisiearthroplastiek te vermijden.

In **Hoofdstuk 9** is het effect van verwijderen van het osteosynthesemateriaal na interne fixatie van een collum femorisfractuur op fysiek functioneren geanalyseerd. Hierover is nog weinig informatie beschikbaar. Na genezing van een collum femorisfractuur wordt het implantaat soms verwijderd, omdat het lokale irritatie en functionele beperking kan veroorzaken. Dat is het resultaat van uitzakken van het implantaat als gevolg van impactie ter plaatse van de fractuur. Het is ook onbekend welke patiënten in aanmerking komen voor verwijdering van het osteosynthesemateriaal. Daarom zijn de karakteristieken van patiënten bij wie het implantaat is verwijderd bestudeerd in een secundaire cohortstudie naast de FAITH studie. Patiëntkarakteristieken en gegevens over QOL (SF-12 en WOMAC scores) zijn verzameld en patiënten bij wie implantaat is verwijderd zijn vergeleken met patiënten bij wie dit niet het geval was. Gematchde paren zijn geselecteerd op basis van patiënt- en fractuurkarakteristieken, evenals pre-fractuur fysiek functioneren. Van 162 patiënten die genezen zijn na interne fixatie is bij 37 (23%) het implantaat verwijderd. Deze patiënten waren jonger (mediane leeftijd 67 versus 72 jaren, P=0,024) en vaker mobiel zonder hulpmiddel voor het ontstaan van de fractuur (100% versus 84%, P=0,008) dan de patiënten met het implantaat *in situ*. Ze hadden ook vaker een evidente uitzakking van het implantaat op röntgenfoto's (54% versus 34%, P=0,035), mogelijk gerelateerd aan een groter deel Pauwels 3 type fracturen (41% versus 22%, P=0,032). De kwaliteit van leven nam sterker toe bij patiënten na implantaatverwijdering (+2 versus -4 punten SF-12 (fysieke component), P=0,024; +9 versus 0 punten WOMAC, P=0,019). De positieve effecten van het verwijderen van het osteosynthesemateriaal op de kwaliteit van leven (met name functie- en ziektegerelateerd) suggereren dat verwijdering van het osteosynthesemateriaal laagdrempelig overwogen dient te worden voor patiënten na interne fixatie als pijn persisteert of functioneel herstel onvoldoende is. Dit effect werd gezien in een studiepopulatie met relatief jonge patiënten die voor het ontstaan van de fractuur mobiel waren zonder hulpmiddel en een evidente uitzakking van het implantaat op röntgenfoto's hadden.

In **Hoofdstuk 10** werd de frequentie, duur en structuur bepaald van de fysiotherapie die patiënten na interne fixatie van een collum femorisfractuur krijgen na ontslag uit het ziekenhuis. Fysiotherapie na heupfractuurchirurgie is belangrijk voor het herstel van onafhankelijk functioneren. Een recente meta-analyse toonde voordelen van een verlengd, geïntensiveerd fysiotherapieprogramma. Weinig studies evalueren echter de frequentie, duur en structuur van de fysiotherapie die in de dagelijkse praktijk wordt gegeven. Om te bepalen welke patiënten wellicht baat hebben bij een langere periode van fysiotherapie werden de karakteristieken vergeleken van patiënten die een korte therapieduur hebben gehad (d.w.z. <6 maanden) met die van patiënten die een langere therapieduur hebben gehad (d.w.z. ≥6 maanden). In een cohortstudie naast de FAITH studie werden alle patiënten

geïncludeerd die minimaal vier fysiotherapiebehandelingen hadden ondergaan in het eerste postoperatieve jaar. De behandelend fysiotherapeuten werden gevraagd een vragenlijst in te vullen over de behandeling van hun patiënt(en). De fysiotherapeuten van 108 patiënten antwoordden. Patiënten kregen mediaan 27 behandelingen over een periode van 20 weken. Functionele oefentherapie en actief bewegen waren de meest toegepaste methoden. Dit is iets minder intensief dan geadviseerd wordt op basis van een recente meta-analyse. De lange behandelgroep had bij de start van de behandeling een significant meer beperkte beweeglijkheid van de heup en significant minder abductie- en extensiekracht dan de korte behandelgroep. De lange behandelgroep werd tijdens de behandelsessies ook meer beperkt door angst. We concludeerden dat beweeglijkheid en spierkracht van de heup bij de start van de behandeling voorspellers zijn voor de duur van de fysiotherapie. Beperkingen door angst om te vallen spelen ook een rol. Met deze factoren dient rekening gehouden te worden bij het opstellen van een behandelplan en tijdens het voorschrijven van een langere periode van fysiotherapie.

Samengevat wordt in dit proefschrift bewezen dat:

- Een gefinancierde, centrale studiecoördinator voor alle studiegerelateerde taken in alle deelnemende centra is een aanbevolen strategie om studieprogressie te verbeteren (Hoofdstuk 2)
- Adequate kennis van de International Conference of Harmonization-Good Clinical Practice (ICH-GCP) richtlijn is van belang bij de uitvoering van een implantaatstudie in de orthopedie of traumachirurgie (Hoofdstuk 3)
- De huidige behandeling van patiënten met een collum femorisfractuur is conform de nationale richtlijn in tenminste 74% van de patiënten (Hoofdstuk 4)
- De huidige behandeling van patiënten met een niet-synchrone bilaterale collum femorisfractuur is uniform in 73-88% van de patiënten (Hoofdstuk 5)
- De totale kosten van interne fixatie bij patiënten met een collum femorisfractuur zijn ongeveer €16.000 en €19.000 na één, respectievelijk twee jaar follow-up (Hoofdstuk 6)
- Interne fixatie bij patiënten met een collum femorisfractuur lijdt tot collumverkorting en secundaire permanente fysieke beperkingen in een meerderheid van de patiënten (Hoofdstuk 7)
- Patiënten na een revisiearthroplastiek hebben een slechtere functionele uitkomst dan patiënten die genezen na interne fixatie van een collum femorisfractuur (Hoofdstuk 8)
- Verwijderen van het implantaat heeft een positief effect op de functiegerelateerde kwaliteit van leven van patiënten na interne fixatie met persisterende pijn of onvoldoende functioneel herstel (Hoofdstuk 9)

- De fysiotherapie die patiënten na interne fixatie van een collum femorisfractuur krijgen bestaat met name uit actief bewegen, functionele oefentherapie en zelfstandig oefenen gedurende 20 weken, waarbij de frequentie minder dan twee keer per week is (Chapter 10)

Hoofdstuk 13 bevat een algemene discussie van de belangrijkste bevindingen in dit proefschrift en de consequenties hiervan op de behandeling van patiënten met een collum femorisfractuur met interne fixatie, inclusief een toekomstperspectief.

Chapter 13

General discussion

Implications and future perspectives

In order to facilitate future research in orthopedic trauma topics it is important to decrease the burden of the logistical and regulatory challenges related to performing multicenter randomized controlled trials. A central financed trial coordinator to manage all trial related tasks in participating sites is a recommended strategy to overcome some of these challenges (Chapter 2). Knowledge on legislation and guidelines (*i.e.,* the International Conference of Harmonization-Good Clinical Practice (ICH-GCP) guideline), as well as insight in factors that could hamper study progression, is important when designing and conducting any trial, to promote efficient trial progress (Chapter 3).

In the past few years many trials have been conducted in order to define the best treatment for patients with a femoral neck fracture.[1-7] Taking this recent evidence into account, one could wonder if the problem of the so-called 'unsolved fracture' is still unresolved. In the Netherlands, treatment of femoral neck fracture patients seems both uniform as well as in adherence with national guidelines in a vast majority of patients (75-88%; Chapters 4 and 5). It seems that only the treatment of a small subgroup of patients may still be topic of debate (*i.e.,* vital patients aged approximately 65-80 years with a displaced fracture). Future studies should focus on defining the best treatment for this specific subgroup of patients.

Another important issue that is still unresolved concerns the best implant for internal fixation (Chapters 4 and 5). The international FAITH trial (Fixation using Alternative Implants for the Treatment of Hip fractures, NCT00761813; Appendix 1) is aimed at resolving this problem, comparing angular stable (dynamic hip screw) with non-angular stable implants (cancellous screws).[8] In March 2014 the international enrollment was closed, after including the 1,111th patient in the trial. The results can therefore be expected in 2016, and will provide information on revision surgery rates, morbidity, mortality, and quality of life.

When deciding on the best treatment of a femoral neck fracture patient, costs may also play a role. Detailed information on health care costs are gaining importance as the burden of health care costs threatens to exceed the financial resources available. The total mean costs per femoral neck fracture patient treated with internal fixation are €16,379 at one year follow-up and €19,425 at two years follow-up (Chapter 6). These costs are comparable with costs published from previous studies in Western societies in general, but lower than costs published in Norwegian studies specifically. The hip fracture care pathways implemented in the Netherlands promoting early mobilization, early hospital discharge, and rehabilitation in a specialized nursing home department or at home, seem successful and contribute to limiting health care costs. Although rehabilitation and physical therapy were important determinants in the total costs, these should not be a focus in reducing costs, as they have proven to benefit patient outcome and independency. Highest costs are generated by patients who underwent a revision to arthroplasty. This reinforces the importance of attempting to reduce

the potentially avoidable risk of a revision surgery by a careful selection of patients for internal fixation, not only for medical reasons, but also economic reasons. After completion of the FAITH trial, costs may be calculated for the more evidence based treatments with internal fixation and these can be compared to render even more economic information.

It is expected that the results of these and other recently published trials will help reinforce a more evidence-based and uniform treatment of femoral neck fracture patients. As the Dutch national guideline on the treatment of femoral neck fractures was published in 2007, it requires an update within the next few years, to include all new evidence available.[9]

In the ongoing debate on the best treatment of femoral neck fracture patients, research has mainly been focused on the technical success of a treatment, defined by fracture healing, revision surgery, morbidity, and mortality. However, focus should perhaps shift towards effects of treatment described in terms of symptom relief, restoring functional ability, and improving quality of life.[10] This can be measured using PROMs (Patient-reported outcomes measures). It is important to realize that disease-specific PROMs (*e.g.,* WOMAC; Western Ontario McMaster Osteoarthritis Index) are probably more appropriate in hip fracture patients than generic health-related quality of life instruments, as they provide more specific information on physical functioning (Chapters 8 and 9). These data should be combined with other objective functional outcome measurements in hip fracture patients, such as measurements of femoral neck shortening/leg length discrepancy, muscle strength, and gait pattern or velocity (Chapters 7 and 8).

The consequences of femoral neck shortening after internal fixation of a femoral neck fracture should not be underestimated, as it results in impaired gait velocity and physical complaints. Attention should be paid to adequate compensation of a shortened femoral neck by prescribing a heel lift, which is currently done in a small number of patients only (Chapter 7). Perhaps there is even a need to develop a new implant that allows for limited impaction at the fracture site only, to a certain maximum extent. The biomechanical rationale behind existing implants such as the dynamic hip screw or multiple cancellous screws is that compression of fracture fragments will stimulate fracture consolidation. However, it has not been proven that unlimited impaction is a requirement for fracture healing. It would be interesting to develop a new implant, that would allow for impaction at the fracture site to a maximum of approximately one centimeter, and see if this promotes functional recovery and gait symmetry, without increasing non-union rates.

Functional outcome should also be considered when deciding on treatment for a femoral neck fracture patient. Salvage arthroplasty following initial treatment with internal fixation is required in approximately 35% of patients.[11-14] It is therefore important to realize that salvage arthroplasty has a significantly worse long-term functional outcome than successful internal fixation (Chapter 8). When considering internal fixation for fitter femoral neck

fracture patients the possibility and consequences of a salvage arthroplasty must therefore be acknowledged and patients should be informed. The data in this thesis may even suggest that surgeons could more liberally consider a primary arthroplasty for patients with displaced (Garden III-IV), sheer (Pauwels 3) femoral neck fractures.

After uneventful healing of a femoral neck fracture, patients sometimes report persistent pain or unsatisfactory functional recovery, caused by the implant. The implant can cause local irritation and functional impairment, especially if it has backed-out as a result of fracture impaction, and is therefore sometimes removed after fracture healing.[15-17] Patients who have their implant removed are younger, more often independent ambulators pre-fracture, have a Pauwels 3 type fracture, and an evident implant back-out on x-rays than patients who do not (Chapter 9). Given the positive effect of implant removal on physical functioning as shown in this thesis, we suggest that implant removal should be considered more liberally in these patients. Perhaps the indication for implant removal after internal fixation of a femoral neck fracture should even be widened. Patients with minimal impairment may also benefit from implant removal. It seems legitimate to evaluate this in a trial-setting, as implant removal proved a safe procedure with minimal risk (Chapter 9). A different solution could lie in minimizing implant back-out and thus minimizing complaints. New implants have been developed that do not back-out into the soft tissue.[18]

In order to promote functional recovery after internal fixation of a femoral neck fracture, physical therapy is provided. Physical therapy is aimed at improving mobility, lower limb strength, and balance, resulting in regained independence in functioning and daily activities. The physical therapy that femoral neck fracture patients receive after internal fixation generally consists of active movement, functional exercise, and independent practice for less than two times a week, during 20 weeks (Chapter 10). This is slightly less intensive than a recent meta-analysis advises.[19] Future studies should try to define the optimal physical therapeutic treatment regimen and focus on evaluating cost-effectiveness of extended therapy. Providing extended therapy to all patients will significantly increase treatment costs and may not be indicated. It is therefore important to define a subgroup of patients who would benefit from an extended or intensified program. Hip range of motion and muscle strength at the start of the therapy were predictors for the duration of physical therapy in this thesis. Restrictions caused by anxiety to fall may also play a role (Chapter 10). Until more data are available, these factors can be used when designing a physical treatment plan and deciding on prescribing extended physical therapy. Evidence-based physical therapy should be incorporated into national hip fracture guidelines in order to stimulate uniform treatment. Improving documentation of physical therapy should also receive attention in guidelines, facilitated by a standard documentation tool (physical therapy road map) that is yet to be developed (Chapter 10).

Future perspectives summarized

Attention and future studies should focus on:

- Defining the best treatment for vital patients aged approximately 65-80 years with a displaced femoral neck fracture, comparing internal fixation (and the various implant types) and hip arthroplasty (*i.e.,* hemi- and total hip arthroplasty)
- Updating the Dutch national guideline on the treatment of femoral neck fractures, including advice on physical therapy
- Including disease-specific PROMs and objective functional outcome measurements (*i.e.,* measurements of femoral neck shortening/leg length discrepancy, muscle strength, and gait pattern or velocity) in future hip fracture research
- Developing a new implant, that would allow for impaction at the fracture site to a maximum of approximately one centimeter, and evaluate if this promotes functional recovery and gait symmetry, without increasing non-union rates
- Compare functional outcome of salvage arthroplasty and primary arthroplasty patients
- Evaluate if implant removal is also indicated for patients with minimal persistent complaints or functional impairment after fracture healing of a femoral neck fracture
- Define the optimal physical therapeutic treatment regimen with a focus on evaluating cost-effectiveness of extended therapy
- Improving documentation of physical therapy, facilitated by a standard documentation tool (physical therapy road map)

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Appendix 1 Summary FAITH study protocol

Contributing authors

List of publications

Dankwoord

Curriculum vitae

PhD Portfolio

Appendix 1. Summary FAITH study protocol

Fixation using Alternative Implants for the Treatment of Hip Fractures (FAITH): A Multi-Centre Randomized Trial Comparing Sliding Hip Screws and Cancellous Screws on Revision Surgery Rates and Quality of Life in the Treatment of Femoral Neck Fractures

Rationale

Hip fractures occur in 280,000 Americans (over 5,000 per week) and 36,000 (over 690 per week) Canadians annually. The number of hip fractures is likely to exceed 500,000 annually in the United States and 88,000 in Canada. The estimated annual health care costs will reach a staggering $9.8 billion in the United States and $650 million in Canada. Hip fractures are associated with a 30% mortality rate and profound temporary and sometimes permanent impairment of independence and quality of life. Worldwide, 4.5 million persons are disabled from hip fractures yearly with an expected increase to 21 million persons living with disability in the next 40 years. Experimental data suggest that cancellous screws offer greater preservation of blood supply, while sliding hip screws provide greater biomechanical stability to bending stresses. While both arguments are persuasive, the impacts of these biologic alterations on outcomes that are important to patients offer more compelling guidance for clinical practice.

Need for a Definitive Randomized Controlled Trial

The rationale for the trial is summarized below. First, although current opinion among orthopaedic surgeons favours the use of cancellous screws over sliding hip screws, there remains sufficient divergence in perceptions and sufficient interest to resolve this issue to warrant a large randomized controlled trial. Second, despite the popularity of cancellous screw fixation, there is a strong biologic rationale supporting the sliding hip screws, a more biomechanically stable construct, in older patients with osteopenia or osteoporosis. Third, while a meta-analysis by Bhandari et al. provides indirect and direct evidence that a sliding hip screw may reduce revision surgery rates, the evidence remains far from definitive. The current best estimate of treatment effect with sliding hip screws is based upon small trials with methodological limitations including unconcealed randomization and lack of blinding. The resulting estimates include wide confidence intervals (*i.e.*, displaced fractures: RRR=27%, 95%CI: 48%, -4%, P=0.08). Whatever approach to internal fixation proves best, a large proportion of patients will continue to need revision surgery that is associated with high morbidity and appreciable mortality.

Objective

The primary objective is to assess the impact of sliding hip screws versus cancellous screw fixation on rates of revision surgery at two years in individuals with femoral neck fractures. The secondary objective is to determine the impact on health-related quality of life (Short Form-12, SF-12), functional outcomes (Western Ontario McMaster Osteoarthritis Index, WOMAC), and health outcome (EuroQol-5D, EQ-5D).

Hypothesis

It was hypothesized that sliding hip screws will have lower rates of revision surgery (primary outcome) and higher functional outcome scores (secondary outcome) at 24 months than cancellous screws.

Study Design

In a multi-centre, concealed randomized trial design using minimization to determine patient allocation surgeons across North America, South America, Europe, Australia, Asia, and Africa participate. Surgeons will use one of two surgical strategies in 1,500 patients who have sustained a femoral neck fracture. The first strategy involves fixation of the fracture with multiple small diameter cancellous screws (*i.e.*, cancellous screws group). The second treatment strategy involves fixation of the fracture with a single larger diameter screw with a sideplate (*i.e.*, sliding hip screw group). Study personnel will monitor critical aspects of peri-operative care and rehabilitation for protocol deviations. Patients will be assessed at hospital admission (baseline), one week, 10 weeks, 6 months, 9 months, 12 months, 18 months, and 24 months after surgery. The primary outcome is revision surgery within two years of the initial surgery. The secondary outcomes include patient quality of life (Short Form-12, SF-12), function (Western Ontario McMaster Osteoarthritis Index, WOMAC), and health outcome (EuroQol-5D, EQ-5D). Revision surgery rates will be adjudicated at regular intervals up to two years.

Netherlands

In the Netherlands 14 hospitals participated and enrolled 250 patients (February 2008-August 2009). Patients were recruited for the Dutch FAITH trial if they (1) were adults aged ≥50 years; (2) had a radiologically confirmed femoral neck fracture (*i.e.*, undisplaced fracture or displaced fracture in ASA 1-2 patients (American Society of Anesthesiologists classification), were aged 50-80 years, with a fracture that could be closed reduced); (3) had a low energetic fracture without other major trauma; and (4) were ambulatory pre-fracture (with or without aid). Patients were excluded if they; (1) had a fracture not suitable for internal fixation (*e.g.*, pathological fracture, rheumatoid arthritis, or osteoarthritis); (2) had associated major injuries of the lower extremities; (3) had retained hardware around the hip; (4) had an infection

around the hip; (5) had a bone metabolism disorder other than osteoporosis; (6) were moderately or severely cognitively impaired pre-fracture; (7) had dementia or Parkinson's disease severe enough to compromise the rehabilitation process; or (8) were not likely to be able to complete follow-up. These eligibility criteria did not interfere with national treatment guidelines.

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Lieve Joost. Jij bent alles wat ik nooit meer voor mogelijk had gehouden. Je bent mijn maatje en ik hoop dat ik de kans krijg nog heel lang met jou van alle kleine dingen in het leven te genieten. Ik wil je nooit meer kwijt.

Curriculum Vitae

Stephanie Maria Zielinski werd geboren op 28 februari 1983 te Doetinchem. Na het eindexamen Gymnasium in 2000 aan het Vincent van Gogh College in Assen begon zij aan haar studie Geneeskunde aan de Rijksuniversiteit Groningen. Tijdens het vierde jaar van haar studie liep zij gedurende 4 maanden een wetenschappelijke stage bij de Trauma Unit van het Johannesburg General Hospital in Zuid-Afrika, waar zij tevens de gelegenheid kreeg haar eerste klinische ervaring op te doen. Tijdens haar studie deed zij ook onderzoek voor het Mobiel Medisch Team van het Universitair Medisch Centrum Groningen. De laatste maanden van haar co-schappen liep zij op de afdeling Traumatologie van het AMC in Amsterdam. In 2006 haalde zij haar artsexamen, waarna zij als arts-assistent werkzaam was op de afdeling Heelkunde van het Erasmus MC in Rotterdam. In 2008 werd zij aangenomen als arts-onderzoeker en begon zij onder begeleiding van prof. dr. Patka aan het wetenschappelijk onderzoek wat heeft geleid tot dit proefschrift. Gedurende 4 jaar was zij studiecoördinator voor de 14 deelnemende ziekenhuizen aan de FAITH studie in Nederland. In 2012 begon zij aan de opleiding tot chirurg in het Erasmus MC (opleiders: prof. dr. IJzermans en dr. Wijnhoven). In 2014 vervolgde zij haar opleiding in het Reinier de Graaf Gasthuis in Delft (opleider: dr. van der Elst). In haar vrije tijd is Stephanie KNHS-jurylid dressuur en gaat zij graag golfen, skiën en reizen.

PhD Portfolio

Summary of PhD training and teaching

Name PhD student: Stephanie M. Zielinski Erasmus MC Department: Trauma Research Unit Department of Surgery	PhD period: January 2008 – December 2011 Promotor(s): Prof. Dr. P. Patka Co-promotors: Dr. E.M.M. Van Lieshout, Dr. M.J. Heetveld

1. PhD training		
	Year	**Workload (ECTS)**
General courses		
BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2008	1.0
Minicursus methodologie van patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen	2010	0.3
Biomedical English writing and communication	2011	5.0
Specific courses (e.g. Research school, Medical Training)		
OTC Clinical research course	2008	1.5
International conferences		
OTA San Diego (oral presentation at investigators meeting)	2009	2.0
ESTES Milan (oral presentation)	2011	2.0
DKOU Berlin (oral presentation)	2013	2.0
OTA Phoenix (oral presentation)	2013	2.0
ESTES Frankfurt (oral presentation)	2014	2.0
National conferences		
ZWOT (oral presentation)	2008	1.0
Assistentensymposium NVT (oral presentation)	2011	1.0
Traumadagen NVT (oral presentation)	2011	1.0
Najaarsvergadering NVvH (oral presentation)	2011	1.0
Traumadagen NVT (poster presentation)	2012	1.0
Assistentensymposium NVT (oral presentation)	2013	1.0
Chirurgendagen NVvH (oral presentation)	2013	1.0
Traumadagen NVT (poster presentation)	2013	1.0

2. Teaching		
	Year	**Workload (ECTS)**
Lecturing		
Lecturing for students TU Delft	2010	0.3
Lecturing in proximal femur fracture course	2013	0.3
Supervising practicals and excursions, Tutoring		
Examination of Basic Life Support for medical students	2009-2010	0.5
Supervising Master's theses (3 students)		
Max Meeuwis	2010-2011	2.0
Karlijn Petri	2010	2.0
Sanne Hidding	2011-2012	2.0