Doctoral theses at NTNU, 2015:342

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ISBN 978-82-326-1345-8 (electronic ver.)
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Printed by NTNU Grafisk senter

Sammendrag på norsk

Bakgrunn: Hoftebrudd er en viktig årsak til sykdom og død med 1.3 millioner brudd årlig i verden og en fortsatt stigende insidens. Risikofaktorer er høy alder, osteoporose og skrøpelighet, og de fleste bruddene skyldes lav energitraumer på grunn av fall. Høy alder, nedsatt funksjon før bruddet og mannlig kjønn øker risiko for et uheldig resultat, mens fall utendørs er prognostisk gunstig.

Utvikling av såkalt ortogeriatriske behandlingsmodeller for hoftebrudd som bruker teknikker og prinsipper utviklet i geriatrien er en måte å bedre prognosen for pasientene. Det er utviklet flere modeller:

1. Konsultasjonsmodeller der pasienten på vanlig måte behandles i en ortopedisk avdeling, men får tilsyn og vurdering av geriater eller et geriatrisk team under oppholdet, og der teamet deretter foreslår tiltak til ortoped.
2. Modeller med felles ansvar der geriater og ortoped inngår i et team som utreder og behandler pasienten og legger en felles plan for videre oppfølging.
3. Geriatrisk team modeller der utredning og behandling (med unntak av selve kirurgien)foregår i en geriatrisk avdeling tilpasset bruddbehandling, og der ortopeder ansvarlig for operasjon, men ellers kun konsulteres ved behov.

Målsetninger for studien: Overordnet mål for studien var å undersøke om bred geriatrisk utredning og behandling (CGC) ga en tilleggsgevinst sammenlignet med tradisjonell ortopedisk behandling (OC).

Målsetninger for denne avhandlingen er:

1. Å beskrive bakgrunn, utvikling og prinsippene bak de orthogeriatriske modellen og hvordan den skiller seg fra vanlig behandling (Artikkel I).
2. Å presentere kliniske resultat (Artikkel II):
    a. Mobilitet fire måneder etter bruddet (primært endepunkt)
    b. Sekundære endepunkt:
        i. Mobilitet etter en og 12 måneder, og p- i-ADL, kognisjon, frykt for å falle, stemningsleie og livskvalitet en, fire og 12 måneder etter bruddet,
        ii. Bruk av helsetjenester første året etter bruddet
3. Finne ut om effekten på mobilitet, p- og- i-ADL og kognisjon var avhengig av alder, kjønn, bruddtype og funksjon før bruddet (Artikkel III).

Metode: Hoftebruddsstudien i Trondheim er en randomisert kontrollert studie basert på ortogeriatri-modell 3 ovenfor. Studien sammenligner standard ortopedisk behandling (OC) med ortogeriatrisk behandling i en egen enhet (CGC). Hjemmeboende pasienter 70 år eller eldre som klarer å gå minst 10m og som har et lavenergibrudd kunne inkluderes, mens pasienter fra sykehjem, høy-energi brudd, patologisk fraktur eller annen sykdom med forventede leveutsikter på mindre enn 3 måneder ble ekskludert. Behandlingen er basert på bred geriatrisk utredning (CGA) og gjennomføres av et tverrfaglig

team bestående av geriater (overlege eller lege i spesialisering), sykepleier, fysioterapeut og ergoterapeut; teamet har regelmessige møter der det lages individuelle behandlingsplaner og settes mål for opphold og klargjør videre behov etter utreise samt behandlingsmål. Behandlingen er helhetlig og fokuserer på tidlig mobilisering, gjennomgang av den enkelte pasient med tanke på bakenforliggende sykdom, medisingjennomgang og diagnose og behandling av komplikasjoner.

Primært endepunkt i studien var mobilitet etter fire måneder testet med SPPB. Pasientene ble også testet på femte postoperative dag, etter en , fire og 12 måneder. Sekundære endepunkt var personlige (p-) og instrumentelle (i-)aktiviteter i daglig livet(ADL) med Barthel Index (BI; 0-20)) og Nottingham Extended ADL Skala(NEAS; 0-66), kognisjon ble testet med Mini Mental Status (MMSE; 0-30) og klinisk demens vurdering (KDV;0-18, 0 best), livskvalitet ble målt med EuroQol 5 dimensjoner (EQ-5d; -0.594-1), depresjon med Geriatrisk depresjonsskala (GDS;0-15), frykt for å falle med Falls Efficacy Scale International (FESI; 7-28) og bruk av tjenester inklusive liggetid sykehus og kommunale tjenester. Vi har også gjort eksplorerende analyser med undergrupper basert på alder, kjønn, brudd type og funksjonsnivå før bruddet.

Analysene er utført som en 2-veis longitudinell mixed model analyse med tid siden brudd og behandlingsgruppe som uavhengige faktorer i analysen og funksjon testet som avhengig faktor. Alder, kjønn og bruddtype er brukt som kovariater. I analysene av undergrupper ble modellen utvidet til en 3-veis interaksjonsanalyse og undergrupper basert på alder, kjønn, bruddtype og funksjon ble lagt inn. Bakgrunnsdata er analysert med kji-kvadrat test og Nevcombes test for forskjeller mellom proporsjoner.

Resultat: 397 pasienter ble rekruttert til studien, 198 til CGC og 199 til OC. Kvinner utgjorde 74 % av materialet, og 60 % bodde alene. Det var ingen signifikante forskjeller I bakgrunnsdata mellom gruppene

Primært endepunkt mobilitet gikk i favør av CGC med SPPB-skår på 5.12 og 4.38 i henholdsvis CGC og OC (CI 0.18 til 1.30; p=0.010). Forskjellen har klinisk betydning. Andre viktige sekundære endepunkt i favør av CGC etter fire måneder var NEAS på 33.59 og 27.42 (CI 2.57 til 9.78; p=0.001); FESI 11.31 og 12.57 (CI -2.27 til -0.27;p= 0.013) og til slutt EQ-5d 0.54 og 0.46 (CI 0.01 til 0.15; p=0.033).

Resultatene ble opprettholdt etter 12måneder og var fortsatt i favør av CGC. SPPB var 5.30 og 4.61 (CI0.10 til 1.28; p=0.023); NEAS 35.20 og 28.81 (CI 2.59 til 10.19; p=0.001); FESI 10.81 og 12.01(CI -2.24 til -0.18; p=0.021) og til slutt EQ-5d 0.52 og 0.45 (CI0.02 til 0.16;p=0.015).

Liggetid (LOS) for index-oppholdet var lenger I CGC med 12.6 i forhold til 11.0 døgn (CI 0.2 til 2.94; p=0.025), men dette ble kompensert med færre liggedøgn påfølgende år 5.63 mot 8.35 (CI -5.48 til 0.04; p=0.053). Bruk av tjenester indikerer mer bruk av institusjonssenger etter behandling i OC, og mer bruk av hjemmebaserte tjenester etter CGC.

Analyser innenfor undergrupper viser en positiv effekt av CGC på etter eller flere delmål i alle undergrupper. Effekten er mest uttalt hos pasienter under 80 år, kvinner, pasienter med intra-kapsulære brudd og pasienter som var i hovedsak funksjonelt uavhengige før bruddet.

Analyser mellom undergrupper viser at pasienter med intra- kapsulære brudd hadde mer nytte av CGC enn pasienter med ekstra- kapsulære brudd etter 4 måneder for p-ADL; BI (gruppeforskjell= 1.51;

p=0.037) og med en trend for mobilitet med SPPB (gruppeforskjell =0.93; p=0.07). Forskjellene ble opprettholdt etter 12 måneder for BI (GD=1.49; p=0.045) og økte for SPPB (gruppeforskjell=1.25; p=0.021).

Konklusjon: I denne randomiserte studien har vi utviklet og testet et nytt behandlingsopplegg for hoftebruddpasienter. Våre resultater viser en overveiende positiv effekt av CGC med forbedrete kliniske resultat på en rekke funksjoner og samtidig reduksjon i bruk av helsetjenester. Effekten er til stede i alle pasientgrupper, selv om pasienter med ekstra-kapsulære brudd synes å ha mindre nytte av CGC enn de andre pasientgruppene.

Acknowledgements

While working with this thesis I was initially employed at the Department of Neuroscience, Faculty of Medicine at The Norwegian University of Science and Technology, NTNU, and when doing the final writing I was employed by Department of Geriatrics, Clinic of Medicine, St. Olav ´s Hospital.

My three years as a research student were financed by a grant from The Norwegian Research Council. The Trondheim Hip Fracture Study was funded by Norwegian Research Council, Central Norway Regional Health Authority, St. Olav's Hospital Trust and Fund for Research and Innovation, the Liaison Committee between Central Norway Regional Health Authority and the Norwegian University of Science and Technology, the Department of Neuroscience at the Norwegian University of Science and Technology, the Foundation for Scientific c and Industrial Research at the Norwegian Institute of Technology (SINTEF), and the Municipality of Trondheim.

First of all I will thank all participants and their next of kin for their participation and contributions to this study; without you there would have been no trial on hip-fracture treatment.

I thank all the involved members of staff at St. Olav's Hospital and especially at the Department of Geriatrics. I also thank the staff members of the Clinic of Emergency Medicine and Prehospital Care, the Department of Orthopedics and the Clinic of Radiology and Nuclear Medicine for the contribution to the study. Special thanks go to Elin Einarsen and Helga Reklev for their contributions to the development and implementation of the clinical methodology used in this trial.

I will especially thank my supervisors Ingvild Saltvedt and Olav Sletvold for inviting me into this study, for their enthusiasm and assistance during the trial and the publication of results in papers. This has been a long journey, and without their motivation and support it might not have ended yet.

I thank the Department of Neuroscience and especially the Research Group of Movement and Geriatrics, GeMS, for their contribution and practical assistance during the process. I thank Jorunn Helbostad for valuable support and important contributions through all phases of my work.

My fellow PhD-students and co-authors Pernille Thingstad and Kristin Taraldsen have my gratitude for their contribution to my work, especially for organizing the logistics and collecting data, for co-authoring, and last but not least, for important mental support during these years.

This study has been a challenging introduction to medical statistics, and I will thank Sarah E. Lamb for her participation in the initial planning of the study and especially her contribution to the statistical analysis plan and for her willingness to share knowledge of good science and "How to get into those big journals". Stian Lydersen has been my local statistician guiding me through the wilderness of SPSS, mixed models and second and third level interaction analyses. Thank you for this, and also thank you for your assistance in helping me to understand and describe what I have done.

Torbjørn Lie has been our designated driver and transported most patients in Trondheim to their scheduled appointments. Without your extra effort our missing data statistics would surely have been different. Thank you very much!

Thanks to my colleague and old friend Ken Klaussen for your work in the study, but more importantly for your continuous education in geriatrics and your great (slightly weird) sense of humor!

Thanks to Marianne for her patience through the study and to my children Tuva Margrete and Amalie for their lack of patience and reminding me what is important in life.

List of papers

I. Saltvedt I, Prestmo A, Einarsen E, Johnsen LG, Helbostad JL, Sletvold O. Development and delivery of patient treatment in the Trondheim Hip Fracture Trial. A new geriatric in-hospital pathway for elderly patients with hip fracture. BMC research notes. 2012;5:355.

II. Prestmo A, Hagen G, Sletvold O, Helbostad JL, Thingstad P, Taraldsen K, et al. Comprehensive geriatric care for patients with hip fractures: a prospective, randomised, controlled trial. Lancet. 2015; 385: 1623-33.

III. Prestmo A ,Saltvedt I, Helbostad JL, Thingstad P, Taraldsen K,Thingstad P, Lydersen S, Sletvold O Who benefits from orthogeriatric treatment? results from the Trondheim Hip-fracture Trial (Submitted for publication)

Contents

Summary in English

Background: Hip fractures are an important cause of morbidity with 1.3 million fractures per year world wide, and the incidence is still increasing. Risk factors for fractures are advanced age, osteoporosis and frailty, and most fractures are a consequence of low energy traumas due to falls. A hip-fracture may have serious consequences for a patient, with loss of mobility, independence including inability to live in own home and even death as the most feared results. Patients being old, with reduced pre-fracture function and male gender have increased risk of an adverse outcome, while patients with out-door fractures have a better chance of recovery.

In orthogeriatric treatment models principles for assessment and treatment of frail elderly patients developed by geriatricians are applied on hip-fracture patients. Several models are developed:

1. Consultation based models where the patient receives treatment in an orthopaedic ward, where a geriatrician or a geriatric multidisciplinary team assess the patient and make recommendations for further treatment.
2. Models of joint care where the geriatrician shares responsibility with the surgeon and treatment is delivered by a multidisciplinary team.
3. Geriatric team models where the patient receives all treatment, except surgery, within a geriatric ward designed for fracture patients, and the orthopaedic surgeon is responsible for surgery and later consulted on demand.

Aims: The overall aim of The Trondheim Hip Fracture Trial was to investigate if comprehensive geriatric care (CGC) was beneficial as compared to conventional orthopaedic care (OC).

Aims of this thesis are:

1. To describe the background, development and principles for the experimental orthogeriatric treatment model and how it differed from conventional orthopaedic treatment (Paper I).
2. To present the main clinical results of the study (Paper II):
    a. mobility at four months after the fracture (the primary end point)
    b. the following secondary endpoints:
        i. mobility at one and 12 months, and p- and i-ADL, cognition, fear of falling, mood and quality of life at one, four and 12 months after the fracture ,
        ii. use of health care services during 12 months of follow-up
3. To study whether efficacy of CGC on mobility, p-and i-ADL and cognition were dependent of age, gender, pre-fracture function and type of fracture in the two groups (Paper III).

Method: The Trondheim Hip fracture trial is a randomized clinical trial (RCT) based on orthogeriatric model 3 comparing standard orthopedic care (OC) in a trauma ward with comprehensive geriatric care (CGC) in a geriatric ward. Home-dwelling patients 70 years or older and able to walk at least 10m suffering from a hip fracture due to low-energy trauma could be included, while patients in nursing-homes, with high-energy trauma, pathological fracture or other disease causing a reduced life expectancy of less than 3 months were excluded. The model is based on a multidisciplinary team

consisting of geriatrician (consultant or resident), nurse, physical therapist and occupational therapist. The team has regular meetings designing an individual care plan including short- and long-term treatment goals for each patient and a plan for discharge. The assessment and treatment is systematic and comprehensive focusing on somatic health including comorbidities and medication, mental health, function and social situation. Early mobilization was important. After discharge from hospital the primary health care had responsibility for the treatment in both groups.

Primary end point of the study was mobility assessed by the Short Physical Performance Battery (SPPB) (0-12) at four months. Secondary end points were personal and instrumental Activities of Daily living (p-ADL and i-ADL) by using the Barthel Index (BI) (0-20) and Nottingham Extended Activities of daily living Scale (NEAS) (0-66), respectively, cognition assessed by using Mini Mental Status Examination (MMSE) (0-30) and Clinical Dementia Rating (CDR) (0-18), quality of life as measured by using the EuroQol-5 dimensions (EQ-5d) (-0.594 -1), mood by Geriatric Depression Scale (GDS) (0-15), fear of falling by Falls Efficacy Scale International (FESI) (7-28) and, use of health care services. Assessments were made at one, four and 12 months; in addition SPPB was made on the fifth postoperative day.

In order to investigate if impact of CGC on SPPB, BI, NEAS and MMSE differed between subgroups of patients, we made post-hoc analyses based on age (70 to 79 or ≥80 years), gender, fracture type (intra- or extra-capsular) and pre fracture function (pre-fracture NEAS <45 or ≥45).

We used two-way longitudinal mixed models analyses with time and group allocation as independent factors and the outcome investigated as dependent factor. Age, gender and fracture-type were co-variates. In the sub-group analyses we did 3-way mixed models analyses with age, gender, fracture type or function added as a factor. Background data where analyzed by chi-square analysis combined with Newcombe´s test for confidence intervals for proportions.

Results: We recruited 397 patients to the study, 198 in CGC and 199 in OC group. There were 74% females and 60% were living alone. Mean age was 83 years. There were no significant differences in background variables between the study arms.

The primary end-point mobility at four months was in favor of CGC with a mean SPPB score of 5.12 in CGC and 4.38 in OC group (CI 0.18 to 1.30; p=0.010). At four months NEAS was 33.59 and 27.42 (CI 2.57 to 9.78; p=0.001); FESI 11.31 and 12.57 (CI -2.27 to -0.27; p= 0.013) and EQ-5D 0.54 and 0.46 (CI 0.01 to 0.15; p=0.033) in the CGC and OC group respectively. For GDS and MMSE there were no differences between groups.

At 12 months the results were maintained in favor of CGC. Mean score for SPPB was 5.30 and 4.61 (CI 0.10 to 1.28; p=0.023); NEAS 35.20 and 28.81 (CI 2.59 to 10.19; p=0.001); FESI 10.81 and 12.01(CI -2.24 to -0.18; p=0.021), MMSE (CI 0.12-2.77; p=0.033) and EQ-5d 0.52 and 0.45 (CI0.02 to0.16; p=0.015) in the CGC and OC groups respectively. For GDS there was a trend in favor of CGC (CI -1.46 -0.02; p=0.06)

Mean Length of stay was longer in CGC with 12.6 and 11.0 days (CI 0.2 to 2.93; p=0.025), but more patients were discharged directly to home after CGC; 47 (25%) against 20(11%); (CI 6.3%-21.4%; p=0.001). The following year after the index stay mean number of days in hospital was 5.63 and 8.35 (CI -

5.48 to 0.04; p=0.053) in CGC and OC respectively. There were more overall use of services indicating more use of institutions such as nursing home and institutionalized rehabilitation in OC, and more use of home-based services in CGC.

Sub groups analysis: Within-group analyses indicate positive effects of CGC in all sub-groups for one or more functional outcomes. The results are most pronounced among patients aged 70 to 79, females, patients with intra capsular fractures and well-functioning patients before fracture.

Between-group analyses at four months show that patients with intra-capsular fractures respond better to CGC than patients with extra-capsular fractures for BI (GD= 1.51; p= 0.037) and a trend for SPPB (GD=0.93; p=0.07). These results are maintained at 12 months for BI (GD=1.49; p=0.045) and increased for SPPB (GD=1.25; p=0.021).

Conclusion: In this RCT we have developed and tested a new clinical treatment program for hip-fracture patients. Our results indicate an overall positive effect of CGC with improved functional outcomes, quality of life and reduction in use of services. The effect is present in all patient groups, but patients with extra-capsular fractures seem to benefit less of the intervention than others.

Abbreviations

ADL- Activities of Daily Living

I-ADL- Instrumental ADL

P-ADL- Personal ADL

APACHE II –Acute Physiology And Chronic Health Evaluation II

BI- Barthel Index

CDR- Clinical Dementia Rating

CGA- Comprehensive geriatric assessment

CGC- Comprehensive Geriatric Care*

CGC- the Comprehensive Geriatric Care group *

CI- Confidence Interval

EQ-5d- EuroQol-5dimensions

FESI- Falls Efficacy Scale International

GDS- Geriatric Depression Scale

GP- general practitioner

GCS- Glasgow Coma Scale

ICD10- International Classification of Diseases version 10

IPLOS-The National Registry for statistics of individual care and nursing.

LMWH- Low molecular weight heparin

LOS- Length of stay

MCID- minimal clinically important difference

MMSE- Mini-Mental Status Examination

NCSP- The NOMESCO (The Nordic Medico-Statistical Committee) Classification of Surgical Procedures

NEAS- Nottingham Extended ADL Scale

NTNU- The Norwegian University of Science and Technology

OC- Standard Orthopedic Care*

OC- The orthopedic care group*

OR- Odds Ratio

OT- occupational therapist

PT- physical therapist

SD- standard deviation

SPPB- Short Physical Performance Battery

START- Screening Tool to Alert of Right Prescriptions

STOP-Screening Tool of Older People´s Prescriptions

TUG- Timed Up and Go

QoL- quality of life

*- **The acronym may refer to either treatment or allocation group. This is reflected by the context.**

1. Introduction:

Fragility fractures are common and serious events affecting mainly elderly people. Osteoporosis and falls are the underlying conditions, and many patients are frail and have co-morbidities and use several drugs.(1) Fragility fractures are a major cause of loss of independence; disability and death of old age.(2-4) Patients with fragility fractures are major consummates of public health services including nursing home beds.(5)

The hip fractures are the most feared of the fragility fractures, because they dramatically affect autonomy and quality of life. (6, 7) Consequences of hip fractures are disturbance of gait and balance, fear of falling and chronic pain. Almost all patients need a walking aid after the hip fracture, a rollator or crouches, and many are permanently dependent of assistance. (8)

New methods to prevent fractures and to improve surgical outcome and the long term result after rehabilitation are developed, but despite such efforts, prognosis is still poor.

1.1 Background:

1.1.1 Epidemiology of hip fractures

World wide there are more than 1.3 million hip fractures every year.(9) The incidence of hip fractures varies considerably between regions and populations. The risk is highest in Scandinavia, with a sevenfold increased risk in comparison with Mediterranean countries. (9) The risk is lowest in China where most fractures occur in men.(9) Data from mixed populations suggest that Africans have a reduced risk compared to other populations, probably due to differences in bone size.(10) More than 50% of hip fractures occur in industrialized countries today, while, due to ageing of populations, a considerable increase is expected in Asia, and by 2050 the majority of fractures will occur there.(11)

There has been a steady increase in the incidence of hip fractures until the mid-nineties. The increase is parallel to the increase in longevity. The average life-span has increased steadily the last 200 years,(12) now reaching 87 years for women and 81 for men in the leading countries (Japan and Iceland).(13)The mean age of the first hip-fracture have increased from 73 years in the 1960s to 79 from in 2008, is expected to increase with 1 year every 5 year period.(14) Even if recent analyses indicate a decline in the incidence of hip-fractures, an increase in the prevalence is expected in the years to come due to the aging of population.(11) As no fracture is better than a well treated fracture, initiatives as “Capture the Fracture” aim to identify patients at risk in order to prevent hip- and other fragility fractures.(15)

Several risk factors for hip fractures have been identified through epidemiological research. Age is the most important risk factor which may be related to many of them being frail, using many drugs and with high prevalence of dementia and osteoporosis.(16)

Osteoporosis is a prerequisite for hip fractures caused by low energy trauma. The definition of osteoporosis is a measured bone mineral density (BMD) T-score below 2.5 SD of normal. (17) The BMD, however only accounts for 40% of the fracture risk in each patient, while the remaining risk is related to

structural attributes of the skeleton. (18) These attributes are not available for regular clinical investigation. Most algorithms to assess fracture risk, use epidemiological factors to improve estimates.(18)Risk factors for primary osteoporosis are advanced age, female gender, Caucasians, low weight, early menopause, sedentary lifestyle, smoking and excess use of alcohol, low serum vitamin-D and little sun-exposure.(19) Secondary osteoporosis are caused by a range of disorders including endocrine (hyperthyroidism, hyperparathyroidism and hypercortisolism), and metabolic disorders (coeliac disease, anorexia nervosa), cancers(lymphomas), drugs(steroids, antidepressants and anti-diabetic drugs) and a range of other disorders.(19) In both primary and secondary osteoporosis there is an imbalance with higher resorption than formation of bone.(20)

Risk factors for osteoporosis and hip fractures are similar, and treatment of osteoporosis protects against hip fractures even if treatment is probably less effective in protecting against hip fractures as compared to other fragility fractures. (17) Calcium and Vitamin-D supplementation is likely to reduce fracture risk, at least in patients living in institutions, (21) while anti- resorptive treatment have failed to show any effect on hip-fractures in patients >80 years of age even if the effect on vertebral fractures is similar to younger patients .(17)

Gender and ethnicity is important. Three out of four hip fracture patients are women.(10) At any given age the risk of a hip fracture are twice in women, but women also have a longer life expectancy than men and are exposed for a longer time. Caucasians have an increased risk of hip-fractures, while the risk is reduced in Africans.(22) Caucasian women have a life-time risk of a hip-fracture of 17%.

Finally, frailty is a strong risk factor for hip fractures. The frequency of frailty varies considerable between studies, but in a large study of women over 65 years approximately one in six was frail.(23) A study in men over 65 years showed that four percent suffered from frailty.(24) Patients with frailty had a 14% risk of hip fracture over 10 years as compared with eight percent for robust women. Frailty will be described in more detail in chapter 1.3.

1.1.2 Epidemiological risk factors for fall

A fall may be defined as an event where a person is coming to rest inadvertently on the ground or floor or other lower level.(25) There is some evidence that a fracture may cause a fall, (26, 27) but in most cases the fall seems to be the causative event.(28) Some risk factors for falls are similar to those of fractures, for instance age and frailty. More than 50% of women aged 75 years or older have had one or more falls over a year period, and 13% of these falls caused a fracture.(29) One study showed that 13 of 308 falls suffered a lower extremity fracture (of which hip fractures are most common in this age group).(29)

Comorbidity is an important risk factor for falls which can be related either directly to disorders causing falls or to side-effects of pharmacological treatment. Disorders affecting balance or muscle strength such as neurological disorders, including stroke and Parkinson's disease increase the risk of falling. Falls among patients with a heart disease may be due to arrhythmia or to side effects of medication, for instance orthostatic hypotension. Drugs affecting the central nervous system including drugs used for psychiatric disorders and insomnia such as antipsychotics, anti-depressants and sedatives are also associated with falls.(30) Recreational substances as alcohol increase risk of falls, and the risk is related

to number of units per week.(31) Acute illnesses, as intercurrent infections, are also important risk factors.

Impaired vision is a risk factor for falls. Disturbances of contrast sensitivity and perception of depth may be important.(32) It is possible that treatment of visual disturbances, for instance by cataract surgery may be beneficial, but further research is needed.(33, 34)

Weather and icy roads and pavements are often mentioned as important factors for falls, and there is an association with low temperature and winter.(35, 36) Most falls causing a fracture are however happening indoors both for community dwelling and for patients in care facilities.(37)

1.1.3 Consequences of a hip fracture

1.1.3.1 Loss of mobility

Mobility is affected in several ways by a hip-fracture. Initially pain and instability of the fragments limits mobility. After surgery the fracture is in general stabilized, and allows for some weight load, but most patients limit the load of the fractured hip as compared to uninjured hip to 50 % immediately after the fracture increasing to 85% after 12 weeks. (38) Most patients suffer from some degree of impairment in mobility even after longer time of observation. This may be due to loss of muscle due to inactivity, nerve damage due to the initial trauma or surgery and reduction of stability of the joint due to biomechanical changes. Studies have shown that 40% loose the ability to walk independently, and in a large study from New York, 14% completely lost the ability to ambulate.(11, 39) In a Swedish study, patients' walking abilities were classified by a 10m walk test as good (able to walk independently <15s with or without a cane), average (able to walk with assistance or walking aid within 30 s) or poor (more than 30s).(40) Only 16% of patients had good walking ability one year after a fracture, and 50% needed a walking aid.(40) In a Norwegian study it was shown that 43% of patients lost the ability to move outdoors from their own home. (8) Mobility is also essential in personal (p-) and instrumental (i-) activities of daily Living (ADL).

1.1.3.2 Activities of daily living

Activities of daily life (ADL) have been measured since the mid-50ties. It is customary to differentiate between personal (or basic) activities (such as personal hygiene or eating) and instrumental activities (or complex) activities (such as outdoor walking, shopping or handling of own economy). Home-dwelling hip fracture patients are likely to have some decline in i-ADL as 55% receive some kind of assistance ,(8) while they had a relatively preserved p-ADL before the fracture.(41) Reduced pre-fracture p- and i-ADL are known risk-factors for adverse outcomes after a fracture.(42) A majority of hip-fracture patients have long-term reduced ADL.(43) Functional outcomes such as improved ADL are essential for independent living and important to evaluate as a potential effect of an intervention.

ADL has a hierarchy where i-ADL tend to be affected before p-ADL, but reduction in either affects risk of falling (44, 45) thereby increasing the risk of a hip fracture. (46) After a hip fracture, decline in both p-ADL and i-ADL have been shown, and 60% of patients need assistance in p-ADL one year after a hip fracture, while 80% report need of assistance in i-ADL.(11) Home-dwelling patients often suffer from

physical rather than cognitive decline, (47) and the need for assistance is partly related to reduction of mobility and p- and i-ADL. A majority of nursing home patients have dementia,(48) and this might affect both p- and i-ADL. Most i-ADL tasks such as ability to prepare a meal, house cleaning or control over own money is no longer performed by nursing home patients and decline is not necessarily perceived as a problem, while reduction of p-ADL as incontinence of urine or feces is more troublesome.

1.1.3.3 Cognition

Diseases affecting cognitive function are associated with dependency, risk of falling and hip fractures.(49, 50) Cognitive impairment may result in loss of muscle strength and balance due to inactivity, increased risk of falling due to risk behavior (walking without necessary aid) and increase of osteoporosis due to malnourishment. Cognitive impairment is the most important risk factor for lost ability to live in own home, (51) and 80 % of Norwegian nursing home residents suffer from dementia. The most important risk factor for cognitive impairment is age.(52) Cognitive Impairment is found to be more important than the fracture itself when family members evaluate care-giver stress.(53)

There are several theories why hip fracture patients often suffer from cognitive impairment after treatment. A large proportion of patients suffer from cognitive impairment before treatment, and the observed reduction in cognition is actually the natural course of a dementia disorder. In a delirium study from Oslo, 42.6% of patients suffered from cognitive decline before suffering a hip fracture.(54) The surgical trauma may cause structural damage to the brain for instance by fat-embolism, (55)and also choice of anesthetic technique may have an impact on the risk of delirium and dementia.(56) . In a study in New York, however, Koval found no difference in outcomes regardless of anesthetic technique.(57)

There is increasing evidence of a strong relation between dementia and delirium in a post operative setting.(58) Acute post operative delirium is a strong predictor of long-term cognitive impairment after hip surgery.(59) Fifty per cent of patients with hip fracture suffer from delirium,(48)and there is an association between delirium and subsequent long-term cognitive impairment after hip fractures.(60-62) Delirium during initial treatment of the fracture with or without known cognitive impairment is associated with increased length of stay (LOS), institutionalization after the fracture and worse functional outcomes.(63)Evaluation of cognition would therefore be an important endpoint when doing longitudinal evaluation of an orthogeriatric hip fracture intervention.

1.1.3.4 Other

Hip fracture patients have a high mortality rate, with a one-year mortality rate after hip fractures up to 30%and a five year mortality-rate >70% for men and almost 50% for women.(4, 64, 65) The difference is probably reflecting a difference in comorbidities and health between genders.(66) One-year mortality varies from >50% for male nursing home patients to < 2% for fracture patients below the age of 70.(67, 68) Patients acquiring the fractures outdoors or related to falls on slippery roads have a reduced mortality.(64) Although mortality risk is lower among those below 70 years, the relative risk of dying is increased as compared to people of the same age without fracture.(69, 70) The risk of dying is largest during the first 3 months after the fracture, but is still increased decades later.(71) In a material from Southern-Norway , overall mortality was 21% after one year and 59% after five years.(72) Cardiac infarction, stroke and cancer are the most important causes of death, but pneumonia and urinary tract

infections are common complications and reasons for in-hospital mortality.(70) In-hospital mortality varies between different studies, from 1.5% to almost 5%.(73, 74) Differences in LOS and discharge practices may explain some of these differences, while differences in treatment strategies also may cause different mortality.

Many patients develop chronic pain after a fracture.(8)Pain affects quality of life and is associated with inactivity and further deterioration in function with increased risk of dependence.(75)

Anxiety and depression are common and affect functional outcomes and quality of life after hip fractures. (52, 76-79) People having moderate or severe depression at the time of a hip fracture had a three-fold risk of loss of independent walking, institutionalization and death as compared to other patients.(78) Fifteen per cent of patients develop depression after a hip fracture.(77) It is likely that inactivity and malnourishment due to depression may contribute to an adverse outcome after a fracture.(78) Psychiatric liaison service may reduce LOS, (80) but otherwise there is limited evidence of improved outcome after a hip fracture by treating the depression.(81) On the other hand use of anti-depressants may contribute to increased fall risk, and an association between anti-depressants and vertebral, but not hip-fractures has been reported.(82)

Fear of falling is a debilitating symptom in many hip-fracture patients. It is associated with pain and depression, but is also independently associated with poor outcome.(83) Patients with severe fear of falling tend to reduce physical activity as do patients with depression and anxiety. (84) Patients with frailty who experience a fall are more likely to have fear of falling than robust fallers. (85)Fear of falling may also stimulate the patient to develop compensatory walking strategies such as increasing stride width and shorter steps and thereby worsen walking ability.(86) Consequences of inactivity and change in walking pattern may create a downward spiral with increasing functional decline that subsequently reduce independent living and reduce quality of life.(87, 88) Strategies to identify and reduce fear of falling after a fracture may therefore be important to improve functional outcomes and improve quality of life.

Hip fractures affect quality of life.(3) A Swedish study reported that the average hip fracture patients had an EuroQol 5-dimension score (EQ-5d) of 0.78 before the fracture and 0.59 four months afterwards.(89) In a time trade-off study of elderly women, loss of independence due to a bad hip fracture(unable to maintain independent living after the fracture) was considered to influence quality of life more than breast cancer or a cardiac infarction.(88)

Hip fracture patients are major consumers of public health services; however there are considerable international and interregional differences.(8, 65, 90) Need for health services depend on age, gender, available informal care and organization of health care.(91) In Norway nursing homes are the main institutional service provided by municipalities. They are publicly funded and administered. The level of care in most cases is similar to a skilled nursing facility. In smaller municipalities, one institution may offer both short- and long term nursing home beds and rehabilitation. In larger cities, as Trondheim, a limited number of large institutions provide rehabilitation, while most of the other institutions have primarily short- and long term nursing home facilities. Sheltered housing where patients live

independently, but have easy access to home care and nurse services is used more frequently and to some degree replaces nursing homes.In a study on hip fracture patients from Malmø, Sweden 61.7% lived in their own home before the fracture, 21.5% had some form of sheltered housing and 9.5% lived in nursing homes.(92) The remaining patients lived in various types of institutions at the time of the fracture.(92) Four months after the fracture 44.7% were still able to live in their own home, 17.4% had sheltered housing and the number in nursing homes had increased to 14.4%. In the Oslo Orthogeriatric Trial one third of patients lived in nursing homes at the time of fracture.(48) After the fracture 16% of previous home-dwelling patients lived in a nursing home.

As for institutions, there is a considerable variation in home-based services. Home nursing services offer medical assistance within the patients´ home, while home-care services offer assistance as house cleaning. Other services are typically safety patrols and meals-on-wheels. There is a considerable increase in use of home-based services and informal care after a fracture.(8)Fifty-five per cent of home-dwelling patients still living at home with no assistance prior to the injury did receive assistance afterwards, and in those who had assistance previous to the injury >50% needed more help afterwards.

There are several estimates of cost of hip-fracture treatment, but the majority only consider hospital service and primarily measuring length of stay.(93-97) An American publication from 2003 estimated a total cost of 81300$, with 44% occurring the first year.(65) In this model 11% of cost was related to the initial stay (8900$) while 44% (35400$) was related to nursing home stays. Studies from other countries with a different organisation of health care may differ considerably, with long stays related to in-hospital rehabilitation or other elements shifting cost between different levels of care.(6) Development of new clinical pathways such as Fast Track Models are likely to reduce costs related to the initial stay, but may generate a cost-shift from hospital to other areas of the health care system.(98)

1.2 Good clinical practice

There are a several guidelines defining good clinical practice in relation to hip fractures. The actual practices still differ between hospitals and nations depending on tradition and available resources. Over the recent years the evidence for adequate treatment has improved due to research , especially audits and national registers have increasing importance in controlling quality of treatment offered.(99, 100) A recent British publication found reduced 30-day mortality from 11 to 8.5% and one-year mortality from 34.1 to28.7% between 2007 and 2011, which is likely related to implementing The UK National Hip Facture Database The consequences are saving of 1000 lives since the database was established. .(101, 102)

“The Blue Book” by the British Orthopedic and Geriatric Societies has been a standard of good clinical practice, and recently a British national guideline based on the same sources has been established.(103, 104) Even if quality is improving, there is still lack of evidence regarding many aspects of hip-fracture treatment.

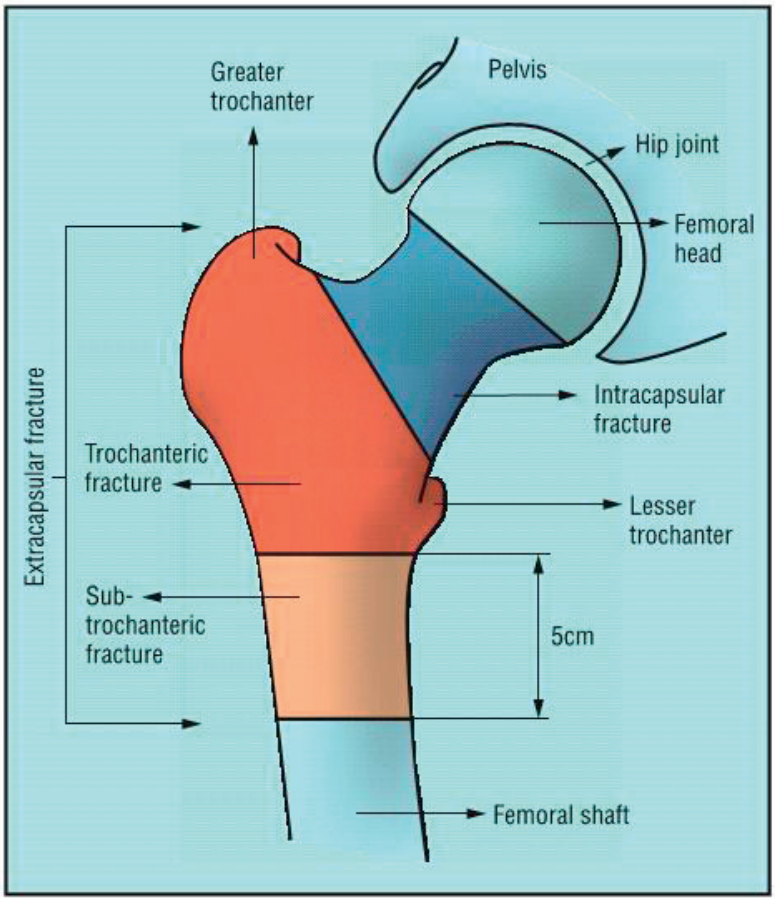
1.2.1 Surgery

There is an agreement that surgery is the treatment of choice for a hip fracture, and there are very few situations where conservative treatment might be considered acceptable.(105, 106) The Girdlestone operation where the femoral head is removed is sometimes used when regular surgery is contraindicated.(107)

There is increasing evidence that time to surgery is essential, (108) and recent guidelines recommend surgery during the same day or next day, if possible.(104, 109) Serious comorbidities including cardiac arrhythmias, electrolyte disturbances, serious disturbances of blood sugar and infections should be treated as soon as possible after admission and sometimes surgery has to be postponed to avoid unnecessary per- and post-operative complications. (104, 110)Complications associated with delay of surgery are infections, including urinary tract infections and pneumonia, pressure ulcers, delirium, deep vein thrombosis and increased mortality.(111)

In recent years, so-called Fast Track Models have been introduced.(112, 113) The key element in these models is standardization of treatment to reduce pre-operative waiting time and total length of stay. Elements of a fast track protocol may for instance be standard blood tests and x-ray, standard intravenous infusions, analgesic treatment, direct transfer to a ward without delay in emergency department and dedicated operating theaters for hip fracture patients. By implementing protocols and delegating simpler tasks to the nursing staff, patients receive surgery sooner and may be discharged at an earlier stage.

Figure 1 Classification of hip fractures (114)

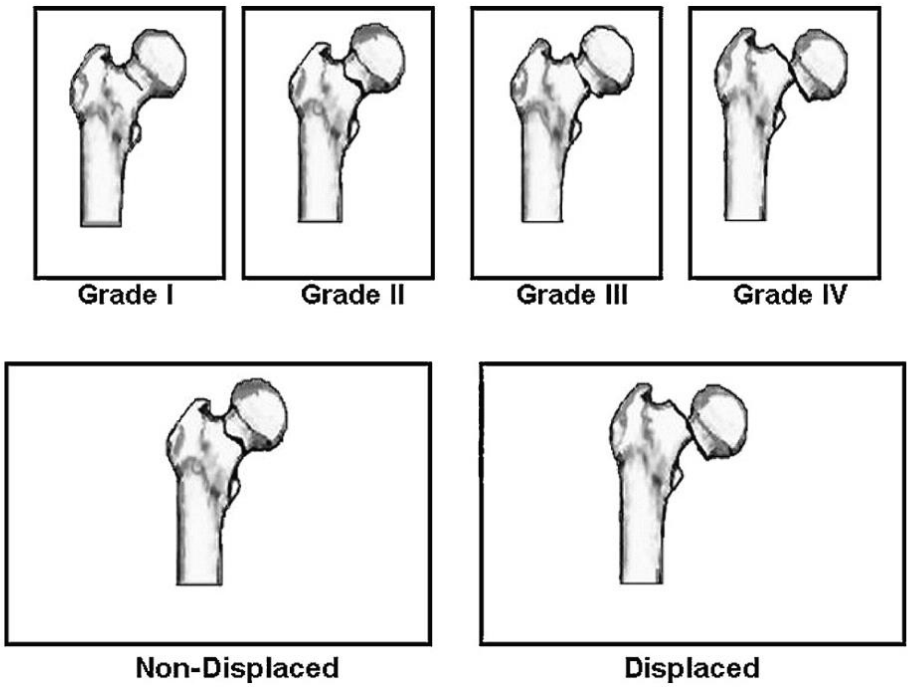


Classification of hip fractures. Fractures in the blue area are intracapsular and those in the red and orange areas are extracapsular

1.2.1.1 Intra-capsular fractures

Fractures of the proximal femur are classified as intra- and extra-capsular fractures. Intra-capsular fractures are divided into displaced (Garden III and IV) and non-displaced (Garden I and II) fractures depending of the angle of the fractured proximal part of the femur and the dislocation of the fragment. The blood supply of the femoral head may be compromised in displaced fractures causing caput necrosis. Therefore current recommendations suggest arthroplasty for displaced fractures ,(115) and internal fixation for non-displaced fractures, especially in younger patients.(103) The surgical trauma is more extensive with arthroplasty, and if the patients are very frail internal fixation may be considered even with a displaced fracture.(115) Occasionally, even the Girdlestone procedure may be an alternative either permanently or temporarily as pain relief for instance where there is strong suspicion of a systemic infection.

Figure 2 Classification of femoral Neck Fractures (116)



Classification of femoral neck fractures into Garden I-IV or dichotomized into Non-displaced or displaced
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1.2.1.2 Extra capsular fractures

Extra capsular fractures are fractures in the trochanter region or the sub-trochanter region comprising of the 5 cm area distal to the lesser trochanter in the femur. Trochanteric fractures may be stable or unstable, often comminute. Sub-trochanteric fractures are often unstable and the prognosis is poor with increased risk of a profound and lasting deterioration of musculoskeletal function.(117). Current guidelines suggest sliding hip screws as t treatment of trochanteric fractures, while for sub-trochanteric fractures sliding hip screws and/or medullary nails are most commonly used.(103)

1.2.2Anesthesia

Both general anesthesia and local anesthesia are acceptable options during treatment of hip fractures.(104, 118) A Cochrane analysis concluded that local anesthesia had lower short term mortality,(118) but the difference was small. In a retrospective non-randomized study from Turkey combined peripheral nerve block was shown to be beneficial, especially for reducing preoperative waiting time as compared to general anesthesia which required more time for medical stabilization before surgery.(119) A Danish group used epidural anesthesia from the diagnosis of a hip fracture until fourth postoperative day as part of their Fast Track model, and report excellent results .(120)

1.2.3 Treatment of pain

Hip fractures are painful, and effective treatment of pain is probably essential for a good outcome.(121) Uncontrolled pain is one of several factors associated with development of delirium; therefore studies focusing on reducing delirium are often focusing on optimal pain management.(122, 123) Even if pain treatment is considered important, evidence is lacking regarding the optimal analgesic regimen.(124)

1.2.3.1 Paracetamol (Acetaminophen)

Paracetamol is considered a safe and relatively effective drug in acute pain management. Most recent studies have paracetamol in the standard pain regimen offered.(124) There are no current evidence showing superiority as compared to other regimes, but most alternatives have more obvious disadvantages.

1.2.3.2 Non-Steroid Anti-inflammatory drugs (NSAIDS)

NSAIDs are potent pain relieving drugs, with a well documented effect as analgesic treatment in an acute setting. They also have a well documented list of potentially dangerous side-effects, especially in the elderly, limiting their use.(125) The most important side-effects are gastrointestinal bleeding, worsening of heart failure and renal failure. New NSAIDs (COX-2 inhibitors) were developed to reduce risk of gastrointestinal bleeding, but were found to increase risk of heart disease.(126)

Despite the risk, some authors advocate more use of these drugs, and report positive effects in studies on control of pain and reducing the need of postoperative opiates.(127, 128)

1.2.3.3 Opiates

Opiates have been the cornerstone of pain treatment for centuries, both chronic and acute. They are widely used, but their equally well known side effects such as chronic constipation, nausea, sedation, delirium, increased risk of falling and urinary retention restricts their use. There are few contra-indications to opiate therapy, and most are relative. Opiates cause respiratory depression, and patients

with respiratory failure should be monitored. Renal failure is associated with increased risk of side-effects to opiate treatment due to accumulation of metabolites.(129) Some patients may develop dependency, but in cases of temporarily strong pain as with a fracture this is hardly a problem. Delirium as a result of pain is more frequent than delirium as a cause of opiate treatment.(130)

There is no strong evidence that regular morphine is inferior to other opiates despite its lower price. Pethidine have clearly more side effects, especially in older patients and should be avoided.(131) It also has a toxic metabolite with serotonergic effects and may cause serotonergic syndrome and interactions with MAO-inhibitors. Tramadol should be avoided in patients with an increased risk of seizures.(132) It also has the indication of moderate pain, and is therefore most likely to be insufficient during the acute phase of hip fracture treatment. Tramadol has its main effect through opiate receptors, but also inhibits the reuptake of serotonin and nor-epinephrine. It may cause serotonergic syndrome, especially when used with antidepressants. (133)Inhibitors of CYP3A4 may affect metabolism of tramadol and its metabolites.(134) Codeine is frequently used in combination with paracetamol (as oral combination drugs for moderate pain) and is metabolized to morphine by CYP 2D6. Eight percent of the Caucasian population has a genetic polymorphism making them poor metabolizers and having no analgesic effect of codeine.(129) Rapid metabolizers have an increased conversion rate of codeine to morphine and may develop toxic levels of morphine by standard doses of codeine.(135) This mutation is relatively rare in an Caucasian population (3%), while as many as 30% of Arabic or North- African origin may have this mutation of CYP2D6.

1.2.3.4 Nerve block

Use of nerve block and local anesthesia can be administered both pre-, per- and post-operatively. It is widely accepted as an alternative to general anesthesia during surgery, and is often used as a safe and effective alternative/supplement to systemic pain medication and. Femoral nerve block is commonly used and is reported even better than standard care regimens, (124) another option is a so-called fascia iliaca block reported to be easier and safer with similar effect.(127)

1.2.4 Medical complications following hip-fractures

Medical complications may develop during the course of a hip fracture. These may be a direct effect of the trauma (for instance anemia due to bleeding), a consequence of treatment (as pneumonia due to immobilization) or other causes (as delirium in frail patients that have multiple potential causes). Standardization of treatment, preventive measures and good routines for follow-up are essential to reduce the risk of complications. Research and identification of best practice is necessary and ongoing, and traditional treatment is revised every year.

1.2.4.1 Delirium

Delirium is defined in the Diagnostic and Statistical Manual of Psychiatric Disorders version 5 (DSM 5)(136) as:

A) Disturbance in attention
B) Impairment in cognition or perception that is not better accounted for by a preexisting dementia
C) The disturbance develops over a short period (hours to days) and tends to fluctuate during the course of the day

D) Disturbances in A and C must not be occurring in the context of a severely reduced level of arousal, such as coma
E) There is evidence that the disturbance is a direct physiologic consequence caused by a medical disorder, medication, intoxication or withdrawal of substances

If the diagnostic criteria above are only partially met, the term sub-syndromal delirium is frequently used.(137, 138) As a rule delirium is reversible, but a protracted course with persisting delirium is common. A meta-analysis found that in patients with delirium during hospital stay, 44% had symptoms at discharge and 26 % had persistent delirium at 3 months.(138) The studies included, however, were in mixed populations and not only hip-fracture patients.

Risk factors for delirium may be divided in predisposing ("The vulnerable patient") or precipitating factors (139) Other authors have chosen to divide these factors in modifiable (intercurrent disease) or non-modifiable factors (for instance age).(140) The mechanisms creating delirium is not fully explained, but a state of reduced acetylcholine and excess dopamine is suggested and sometimes combined with a inflammatory cascade affecting the central nervous system.(136)

Delirium affects a large proportion of hip fracture patients, in some materials over 50%.(48, 60) The frequency of delirium after a hip fracture is similar to delirium after surgery for aortic aneurisms or coronary bypass.(141) In patients without known dementia, delirium during hospitalization for a hip fracture is associated with increased risk of dementia during follow-up.(60) It is also associated with increased LOS, reduction in ADL and increased use of nursing homes.(142)

Clinically, delirium may present as hyper active where the patient is agitated, unable to find rest and may even be aggressive to care-givers; hypoactive where the patient is quiet with a fluctuating consciousness, often bed-resting; or a mixture of these (143) Hallucinations may be present in both hyper and hypoactive delirium. The hyperactive delirium is fairly easy to recognize, while hypoactive delirium may go unattended. Several assessment tools to diagnose delirium such as CAM (Confusion Assessment Method) have been developed and are used extensively in different settings.(144)

Treatment of the underlying disease is important to prevent delirium. Maintaining physiological homeostasis by ensuring oxygen saturation, preventing anemia, control of temperature and blood-pressure did reduce the frequency of delirium in a Swedish study, but failed to identify an effect of one single element.(123) Several studies have shown an effect of pain reduction on the frequency of delirium.(130, 145) Opiates are in general recommended (except pethidine).(130, 146) Other elements proven to be effective is environmental adaptions of the ward by systematic orientation of patients, mental stimulation by access to papers or news, assistance of eating and drinking if necessary, ensuring vision and hearing by access to glasses or hearing aid/ speech enhancer and finally ensuring sleep by adapting the environment (dimmed lightning, reduction of noise) or access to sedatives.(147) Some authors advocate prophylactic use of antipsychotic drugs as haloperidol in high-risk surgical patients.(63) Finally, recent guidelines also address the need to focus on elimination to avoid constipation or urinary retention.(148)

1.2.4.2Anemia and transfusion

Transfusion of blood between a donor and patient has been a medical option since the middle of the 19th century.(149) Arguments for treatment in hip-fracture patients have been patient welfare and reduced risk of delirium when correcting anemia,(122) while arguments against transfusion have been religious, risk of infection (for instance HIV and hepatitis B and C), unnecessary immunization, cost and little evidence of actual benefit of the treatment.(150) Isolated transfusion as a prophylactic treatment of delirium has failed to show any effect.(151) Persistent anemia have been used as an argument of failure to reach mobilization goals, but correction of anemia have not been shown to improve functional outcome in short-term or long term studies.(152, 153) There are reports indicating effects on complication and mortality by a liberal transfusion strategy with a treatment goal for hemoglobin (HgB) above 10 g/dl, (152) and a recent publication found effect on p-ADL but not on QoL by transfusion with a liberal threshold of 11.3 as compared to 9.7 for HgB.(154) Currently the question of when to transfuse remains unanswered.

1.2.4.3 Prophylactic antibiotic therapy

The benefit of prophylactic antibiotic therapy is well documented in hip fracture surgery,(155) and especially in joint replacement. It reduces infections in implants and also protects against urinary and respiratory infections. Any regimen can be used as long as Minimum Inhibitory Concentration (MIC) is maintained from start of surgery to the final closing suture. Single dose regimens are not inferior, and oral treatment is as effective as other methods of administration.(155) The risk of complications seems low, but use of prophylactics may influence resistance pattern of bacteria.(156)

1.2.4.4Anti-thrombotic therapy

Hip fractures are associated with increased risk of deep vein thrombosis and pulmonary embolism related both to the trauma, surgery and immobilization. There is evidence that prophylactic treatment with heparin or low molecular heparin (LMWH) reduces the risk of thrombosis.(157) Studies comparing LMWH with other agents (vitamin-K antagonist, Factor Xa inhibitors and Direct Thrombin inhibitors)indicate a slightly increased risk of bleeding with LMWH, but the level of evidence is limited.(158) For mechanical devices as stockings, there is currently no evidence of effect.(159)

1.3 Geriatric care

The term geriatric medicine was suggested by an Austrian Immigrant to the USA, Ignatz Leo Nascher, who also suggested for the making of a new specialty.(160) In 1947 the British Geriatric Society was founded, first under the name “The medical society for the care of the elderly”, with the purpose to improve research in the field of geriatrics. At this time several clinics and hospitals in UK had started programs for improving outcome for old people with complex disorders.(161) Several important aspects were addressed early in the process: 1. atypical presentation of common disorders in elderly; 2. a holistic approach; 3. interdisciplinary treatment and teams; 4. rehabilitation; 5. focus on caregiver stress; 6. education. These six elements are still the baseline of geriatric medicine.

1.3. Geriatric patients

Geriatric patients are generally old, but age is not the most important factor when identifying the geriatric patient. The typical geriatric patient is frail, has multiple comorbidities and is functionally

declined.(162) Due to their comorbidities, polypharmacy is common, but also underutilization of treatment. The functional decline often involves impairments in mobility, cognition and p- and i-ADL. These characteristics are often also found among hip fracture patients that in many ways may be characterized as geriatric patients. An earlier publication have identified three hip fracture populations, 1: home dwelling outdoor fallers (healthy),2: home-dwelling indoor fallers (at risk) and 3: nursing-home patients.(41) It is customary to consider population 2 and 3 as "geriatric", but the evidence for this assumption is limited.(41)

Frailty is an important concept in geriatric medicine and can be defined as a state of increased vulnerability to stress due to reduced physiological reserves and physiological dysregulation in multiple systems.(162) Each component of frailty may be subclinical, but the accumulation of physiological reduction may cause the clinical entity of frailty.(162) Frailty is associated with age, female gender, functional disability and comorbidities, but is a separate entity. Clinically, frail patients often presents with weight loss, loss of muscle strength, sarcopenia, fatigue, reduced physical activity and reduced gait speed. (162) Frailty increases the risk of a poor outcome after a stressful event and is associated with fear of falling, increased risk of falls.(23)and increased risk of a fracture after a fall. Associated factors as low BMI are important, because low BMI and frailty increases risk of fracture more than eight times. (23) Frail patients are often complex,(163) with functional decline and comorbidities. Specialized care and guidelines focusing on single diseases or single functions often fail to address the complexity. An interdisciplinary, holistic approach as given in geriatric medicine is often necessary to obtain clinical improvements. Even if each intervention may seem small, the accumulated effect of this whole person approach may improve health and increase the patient's capacity to overcome perturbations.

1.3.2 Comprehensive geriatric assessment

The comprehensive geriatric assessment is the fundament of all geriatric treatment and care.(163) This consists of a systematic investigation of physical, psychological, functional and social status performed by a multidisciplinary team consisting at least of a geriatrician, a geriatric nurse and a physical therapist working together and creating a joint plan for the patient. Other members in a team may be an occupational therapist, social worker or a dietician. Use of standardized tests for investigations over a range of domains is common. Early discharge planning in close collaboration with the patient and next of kin and the primary health care is important, as is early mobilization and rehabilitation. This assessment should generate a management plan defining short- and long term goals including hospital care, a plan for rehabilitation and the need for follow-up after discharge. The comprehensive geriatric assessment often includes an ambulatory follow-up when returning home.(164, 165) In Norway, ambulatory follow-up is mostly done by a team from the municipality. This model have been examined in several studies and meta-analysis, and is found to reduce mortality, morbidity and reduce need for institutional care.(165)

1.3.3 Orthogeriatric treatment

Patients with fragility fractures and especially hip fractures share many features with geriatric patients. In orthogeriatric treatment methods developed in geriatric medicine are applied on patients suffering from fragility fractures. Today, the key element is comprehensive geriatric assessment combined with focus on optimal surgical timing and treatment of the fracture.

The special needs of hip fracture patients have been recognized for a long time. The first orthogeriatrician was Lionel Cosin, a surgeon working with rehabilitation. He was present at the founding of the geriatric society at St Johns Hospital, London, in 1947,and thereby recognizing hip- fractures as a geriatric disease.(166) Later Devas (orthopedic surgeon) and Irvine (geriatrician) developed an acute care model with shared care between orthopedic surgeons and geriatricians where early surgery was followed by a geriatric intervention and focusing on early mobilization.

Different models of orthogeriatric care for hip fractures have been developed, but so far the evidence of effect has been limited and to some degree conflicting. There are few publications presenting long term outcomes and economic considerations. (167-169) Today, literature describes three to five different models for orthogeriatric care, (170-172) with some overlap between the models. An overview of models, interventions and results are given in Table 1, section a, b and c.

1. **Geriatric consultations in an orthopedic ward**

a) Liaison service

The simplest model is the orthogeriatric liaison service. In this model the surgeon, by demand, contacts the geriatrician for a consultation while the patient is in hospital.(173) The geriatrician makes a formal investigation of the patient, identifies problems and suggests a solution. Changes in treatment and follow-up are then performed by the surgeon or GP, if indicated. This model is simple, and needs little extra resources if a geriatric ward is present at the hospital. However, no study has shown any effect in regard of improved results so far.

b) Regular consultations

In this model, a geriatric team investigates all patients as a part of the routines of the orthopedic ward. The consultation may take place once or repeatedly during the stay. It may or may not include a multidisciplinary investigation. An RCT performed in Glasgow showed that patients who were offered geriatric consultations as a part of the daily routine had more diagnoses at discharge, but the treatment did not affect outcome or length of stay.(174) As many as 20% of the control patients were also investigated by geriatricians. Education of surgeons during the study may also have affected outcome. A study in Canada evaluating a multidisciplinary team doing regular rounds twice a week found no significant effect on death, ambulation, transfers from bed to chair or ability to stay in own home.(175) The study also included nursing home patients which may have affected the outcome and the potential for improvement

Table 1a Orthopedic ward with geriatric consultation

Study	Design	Intervention	Population	n	Age(mean)	Outcomes	LOS	Follow-up	Result
					Intervention/Control		Intervention/Control		
Gilchrist et all(174) GB 1984-86	RCT	Postoperative inpatient orthogeriatric rehabilitation service with consultation by geriatrician	Women 65+	374	82/81	Mortality, LOS, quality of care	44.0/47.7	6 months	No statistical difference for LOS or mortality. More co-morbidity identified in geriatric group.
Kennie(93) GB (1988)	RCT	Postoperative rehabilitation with consultation of geriatrician	Women 65+	108	79/84	LOS, mortality, physical independence, discharge destination	24 (median)/41(median)	None after discharge	Improved function and more patients returned to own home. Reduced LOS
Naglie(175) Canada (1993-97)	RCT	Multidisciplinary postoperative care with daily medical consultation and multidisciplinary rounds twice a week	70+	279	84/85	LOS, physical performance, mortality, place of residence	29.2/20.9	3 and 6 months	Increased LOS. Trend towards lower mortality, better ambulation and more patients living in own home in patients with mild cognitive decline
Shyu(167, 168, 176-179) Taiwan (2001-03)	RCT	Consultations by team with geriatrician and geriatric nurse in orthopaedic ward	60+	162	77/79	LOS, mortality, ADL, mobility, mood, muscle strength, quality of life	10.1/9.7	3,6,12, 18 and 24 months	Improved ADL, less depression and malnutrition, improved quality of life. Patients with protein-energy malnutrition had increased benefit of a multidisciplinary program
Shyu(180, 181) Taiwan (2005-10)	RCT (3 arms)	1. Multidisciplinary program including geriatric consultation. 2. As 1 +program for fall, depression and malnutrition post discharge 3. standard	60+	299	76/77	ADL, mobility, mood, pain quality of life	7.9 to 8.5 (not specified which arm had the longer stay and not statistically different)./7.9 to 8.5	3, 6 and 12 months	The two intervention arms improved in mobility and different aspects of quality of life as compared to standard care. Patients in the post discharge program had more pain during the program.

		orthopaedic care							
Incalzi(94, 182) Italy (1985-90)	Historical controls	Geriatric consultation as part of routine in orthopaedic ward	70+	761	-/-	LOS, mortality, operation rate	26.2/32.9	No	Reduced LOS and in-hospital mortality. More patients operated
Deschodt(183, 184) Belgium (2007)	Quasi-randomized	Geriatric consultation team	65+	171	80/81	Function, LOS, mortality, readmissions and nursing home	11.1/12.4	6 weeks, 4 and 12 months	No differences found
Marcantonio(122) USA (2001)	RCT	Geriatric consultation	65+	126	78/80	LOS, Frequency of delirium	5(median)/5(median)	No	Reduction of delirium

2. Models of multidisciplinary care in an orthopedic ward

a) Co-managed care

Models where orthopedic and geriatric doctors have shared leadership over the orthogeriatric unit, is called a co-managed model.(185, 186) Decisions regarding the patients are taken by the multidisciplinary team, with both medical professions present. Some units with co-managed care treat patients from the emergency room to discharge from the hospital , while others are in-hospital rehabilitation units with focus on post-operative care and early rehabilitation.(187)

There are a limited number of reports on evaluation of co-managed care. The group in Rochester comparing their data with a national average found reduced length of stay without increasing number of readmissions and reduced number of complications.(188) Tarazona-Santabalbina reports a low readmission rate, but is only comparing with previous publications from other countries.(189)

b) Clinical pathway

A clinical pathway is a model fairly similar to the co-managed model where geriatricians, surgeons and the orthogeriatric team share responsibility for the patient.(190) However, the unit is organized as an assembly line with stations that administer different elements of treatment. Each profession involved has full responsibility for their station. The pathway has predefined standards which limits individualized treatment. In the end, all information is collected in a united, multidisciplinary report.

Again, the evidence of improved results is limited. The NYU Hospital for Joint disease has had a clinical pathway for hip fractures since 1990. In 2004 they published results based on comparison with historical controls indicating reduced length of stay (21.6 to 13.7days) and a surprisingly low in-hospital mortality (5.3 to 1.5%) and one year mortality (14.1 to 8.8%), but found no effect on ambulation, need of surgical revision or discharge status.(190)

	Table 1b Multidisciplinary care in an orthopaedic ward								
Study	**Design**	**Intervention**	**Population**	**n**	**Age (mean)**	**Outcomes**	**LOS**	**Follow up**	**Results**
					Intervention/control		Intervention/Control		
Koval et al (190-193) USA (1990-2014)	Historical controls	Multidisciplinary clinical pathway with preoperative evaluation by medical doctor (no geriatrician).	65+	1065	80/80	LOS, mortality	13.7/21.6	2 years	Reduced LOS and in-hospital mortality. Improvement of quality as more patients were treated according to best practice.
Lundstrøm(194) Sweden (1993)	Historical controls (2 control groups)	Postoperative co-managed care combined treatment and rehabilitation unit	65+	49	79/80	LOS, delirium, functional outcomes, return to previous place of residence	12.5/17.4 and11.1	6 months	Reduced delirium and improved function (mobility)
Fisher et al(195) Australia (1998-2002)	Historical controls	Multi-disciplinary model with co-managed care	60+	951	81/82	Complications, LOS, discharge destination, quality of care	10.8/11.0	6 months	Improved quality of care, reduced in-hospital mortality and complications
Day et al (95, 196) Australia (1994)	RCT	Multidisciplinary care from admission compared with postoperative care in geriatric management unit	55+	71		LOS, mortality, level of recovery, adverse events and mobility	21.0/32..5	1, 6 and 12 months	Reduced LOS and improved long term function (modified BI)
Khan et al(197) GB (1992-96)	Historical controls	Multidisciplinary co-managed care	Elderly	745	82/81	LOS, mortality, discharge destination	26.9/26.1	Discharge	No differences
Roberts et al (198) GB (2000-01)	Historical controls	Integrated care pathway. Details not described	65+	781	83/83	LOS, ambulation at discharge, complications, discharge destination, mortality, readmissions	22.5/16.4	1 month	Improved ambulation, increased LOS. No difference for other outcomes.
Cogan et al(199) Ireland (2006)	Historical controls	Co-managed care starting at admission	65+	201	82/75	Mortality (in-hospital and one- year), LOS, institutionalization, dependency	30.3/23.1	12 months	Reduced in- hospital and one year mortality increased LOS and institutionalization.
Vidan et al (200) Spain (1997)	RCT	Co-managed care with control and intervention patient mixed in the same ward	65+	319	81/83	LOS, mortality, complications, ADL	16/18	Discharge, 3, 6 and 12 months	Reduced in-hospital mortality, improvement in function at 3 months. No effect after 6 and 12 months

Khasraghi et al (201, 202) USA (1995-2000)	Historical controls	Clinical pathway	65+	510	80/80	LOS, mortality, complications, time to surgery and discharge information	5.7/8.1	Discharge	Reduced LOS, reduced time to surgery and fewer complications
Friedman et al (68, 186, 188, 203, 204) USA (2004-14)	Historical controls other centres	Co-managed care	60+	758	85/-	LOS, mortality, reoperations, complications, time to surgery	4.6/8.3	12 months	Reduced LOS, time to surgery and one year mortality. Less post-operative infections
Ventura et al (205) Italy (2011)	Retrospective pragmatic study	Orthogeriatric care against other models	65+	5520	84/-	Time to surgery	-	-	Hospitals with a hip fracture program and orthogeriatric treatment had reduced time to surgery
Pioli et al(206) Italy (2008-09)	Cohorts (3 hospitals with different ortho-geriatric models)	Co-managed care, but some variation between models in Emilia-Romagna	70+	806	86/-	Time to surgery, LOS, mortality , ambulation, ADL, effect of rehabilitation (early intensive rehabilitation(y/n) and/or post-acute rehabilitation(y/n))	11,5/14.6/11.6-	12 months	Time to surgery, early intensive rehabilitation and post- acute rehabilitation is associated with improved one-year mortality. No effect of post-acute rehabilitation without early mobilization
Lau et al (96) Hong Kong (2007-09)	Historical controls	Co-managed care	60+	964	83/-?	mortality ,LOS, cost	6.1/12.1	1 month	Reduced LOS, less complications including reduced mortality. Reduction of cost
Ho et al(207) Hong Kong (2004-06)	Historical controls	Co-managed care	65+	554	83/82	Mortality, LOS, time to surgery, cost-effectiveness	8.3/9.7	12 months	Reduced LOS, time to surgery, in-hospital and 12 months mortality and reduced in-hospital cost
Leung et al (208) Hong Kong (2004-06)	Historical controls	Co-managed care	60+	548	83/83	Mortality, LOS, time to surgery, complications and functional status	9.3/10.8	1, 3 and 12 months	Reduced LOS, 1 and 12 months mortality and improved ambulation and independency at 12 months
Suhm (209) Switzerland (2010-11)	Historical controls	Co-managed Care	65+	493	84/84	LOS, change in residential status, complications and mortality	8.6/11.3	12 months	Reduced LOS and in-hospital complications
Doshi et al(210)	Observati	Co managed care with	60+	219	81/-	LOS, mortality ,	10/(14)	12 months	Patients recover to 95%

Singapore (2011-12)	onal (Historical control LOS)	integration of care manager				functional status			of pre-fracture mobility. reduced LOS,
Kammerlander et al(170, 185, 211, 212) Ostria (2009-11)	Observational, results compared with national register	Co-managed care for all fragility fractures. 1/3 with hip fractures	70+	529	87/-	LOS, complications, return to pre-fracture residence	11.3/12.6	3 months	Less complications and more patients returning to pre-fracture residence
Bhattacharyya et al (213) GB (2010-11)	Historical controls	Preoperative geriatric liaison service and co-managed postoperative care	65+	523	83/83	Staff satisfaction; LOS, mortality, return to residence before admission	19.5/25.0	No follow up after discharge	Increased number of patients returns to pre-fracture residence. Improved staff satisfaction with communication with patient family and discharge planning
Tarazona-Santabalbina et al (189) Spain (2004-08)	Observational (comparison with national data)	Preoperative co-managed care	69+	1363	83/-	Mortality, LOS, ADL, ambulation, readmissions	8.9/-	Discharge, 1, 6 and 12 months	Reduced LOS as compared to national average. Lower rates of readmission as compared to other publications
Dy et al (214) USA (2007-08)	Historical Controls	Preoperative co-managed care	Any	306	82/82(as for intervention)	LOS, complications, readmissions and mortality	8.90/9.06	Discharge , 90 days and 12 months	Less complications and readmissions
Gregersen et al (215, 216) Denmark (2003)	Historical controls	Preoperative co-managed care	65+	495	83/82	LOS, mortality	13/15	Discharge,3 , 6 and 24 months	Reduced LOS
Wagner et al (217) Chile (2007-11)	Historical controls	Preoperative co-managed care	65+	275	85/84	LOS, mortality, complications	9/8	3,6,12 weeks and 6,9 and 12 months	Increased detection of complications (delirium and anaemia), no difference in LOS or mortality.

3. Models of multidisciplinary care within a geriatric environment

a) Geriatric care with orthopedic consultations

In this model, geriatricians and the orthogeriatric team organize the entire care pathway, with orthopedic surgeons performing surgery, and assess fracture specific problems, but otherwise have limited responsibility for the treatment.(218, 219) This model recognizes the fact that except for the surgical treatment of the fracture, the hip fracture patients have mainly geriatric problems which probably are most optimally handled by geriatricians and a geriatric multidisciplinary team.

This model has been evaluated with a pseudo-randomized design where patients entered the experimental model or standard care depending of available beds. Improved functional outcomes, survival and cost-effectiveness have been shown. (169, 220)

Table 1c Orthogeriatric in-hospital care led by geriatricians with orthopedic consultations

Study	Design	Intervention	Population	n	Age	Outcomes	LOS	Follow up	Result
					Intervention/ control		Intervention/ Control		
Adunsky et al (169, 218, 220-227) Israel 1999-2014	Quasi randomized	Acute care multidisciplinary orthogeriatric treatment unit	60+	>3000	82/80	Mortality, LOS, ADL, mobility, cost-effectiveness, other	26.9/31.9	12 months	Reduced LOS, mortality and improved functional outcomes in intervention group.
Gupta et al (97) GB 2011	Historical control	Pre- and post operative geriatrician led acute care, co-managed orthogeriatric unit with pre-operative fast track	50+	294	81/82	LOS, time to surgery	15.1/ 19.3	Discharge	Reduced LOS, more patients operated within 48 hours, but not within 36. Development of model gave an improvement of care (not defined as an outcome).
Miura et al (228) USA 2001-02	Historical control	Pre- and post operative acute care geriatrician led clinical pathway	55+	163	80/80	LOS, time to surgery, hospital costs	4.6/6.1	Not reported	Reduced LOS and cost
Gustafson et al (142, 194, 229-235) Sweden 2000-02	RCT	Early postoperative geriatrician led care program with rehabilitation	70+	199	79/80	LOS, mortality, p- and i-ADL, delirium, falls	30.0/40.0	4 and 12 months	Reduced LOS, falls, reduced occurrence and length of delirium, improvement of ADL,
Mazzola et al (187, 236) Italy 2007-09	Observational/quasi randomized	Geriatrician led orthogeriatric care comparing pre- and postoperative admission in orthogeriatric unit	65+	261	84/84	LOS, time to surgery, in-hospital mortality, mobilization time, complications	13.1/13.6	Discharge	Reduced time to mobilization with preoperative admission. No difference in other outcomes.
Watne et al (48, 237-239) Norway 2008-10	RCT	Pre- and post operative geriatrician led acute care model	70+	329	84/85	Cognition , delirium, , mobility, mortality, ADL, place of residence and weight	11/8	4 and 12 months	Improved mobility in home-dwelling patients; increased LOS, no effect on cognition but less patients discharged with on-going delirium

1.3.4 Rehabilitation after a hip fracture

The concept of orthogeriatric care has to a large extent been invented in rehabilitation facilities, and some of the studies on postoperative in-hospital orthogeriatric services described above may more or less be considered as rehabilitation.(93, 235) Several approaches to organize and also minimize the period of rehabilitation have been proposed, but the evidence for what is the better is limited.(111) The conclusion in a Cochrane review on multidisciplinary rehabilitation is that at least it is not harmful. (240) The routines for rehabilitation depend on traditions and available funding more than evidence. Early mobilization and physical therapy is found to be beneficial.(241, 242) The treatment chain of hip fractures include the initial therapy including surgery followed by in-hospital rehabilitation, sometimes in the ward where patients were admitted for the fracture, or the patients are transferred to an in-hospital rehabilitation unit shortly after surgery.(230) Other options are specialized rehabilitation facilities doing hip-fracture rehabilitation or rehabilitation in a skilled nursing facility depending on availability of organization and competences.(243) Most patients in Norway are treated either in a post acute specialized rehabilitation center or receive general rehabilitation in an institution similar to a skilled nursing facility.

A third option is home based rehabilitation where the patients receive physical therapy at home or in an out-patient clinic.(244) The content of rehabilitation may vary, but most programs focus at improving muscle strength, balance and other aspects of mobility. Norway has a public health care system, and rehabilitation is available for all patients in principle regardless of economy or insurance.

This thesis focuses on acute orthogeriatric assessment and care with just initiation of rehabilitation as part of the process. Therefore, the more detailed aspects of geriatric rehabilitation will not be presented.

1.3.5 Orthogeriatric treatment in Trondheim

The Geriatric Department in Trondheim was established in April 1994. Between October 31, 1994 and November 13, 1995, a large RCT comparing outcome of geriatric patients treated in a nine-bed geriatric evaluation and management unit with similar patients in a general medical ward. (245) The results were in favor of the geriatric unit with improved survival and increased possibility of living at home. The unit now consists of 15 beds and an out patient clinic. The unit employs four senior consultants in geriatric medicine, and four residents as well as a multidisciplinary staff with nurses, assistant nurses, occupational- and physical therapists. Over time the geriatricians at our hospital had the idea to establish an orthogeriatric ward. The opportunity was given during a period of building a new hospital forcing the trauma unit temporarily to reduce their capacity with five beds due to lack of space. These beds were established in the geriatric ward with funding from the Orthopaedic Department. This gave the opportunity to assess model 3 (known as "The Sheba-model") in a RCT. This was also based on a literature review as described previously, the most promising model for orthogeriatrics that needed to be evaluated through a randomized design.(218)

Details on the rationale for and development of the treatment in the orthogeriatric ward are described in paper 1.

2. Aims of the thesis

The overall aim of The Trondheim Hip Fracture Trial was to investigate if comprehensive geriatric care (CGC) performed in an orthogeriatric ward was beneficial as compared to conventional orthopaedic care (OC) in an orthopaedic ward.

Aims of this thesis are:

1. To describe the background, development and principles for the experimental orthogeriatric treatment model and how it differed from conventional orthopaedic treatment (Paper I).
2. To present the main clinical results of the study (Paper II*):
    a. mobility at four months (the primary end point)
    b. the following secondary endpoints:
        i. mobility at one and 12 months, p- and i-ADL, cognition, fear of falling, mood and quality of life at one, four and 12 months ,
        ii. use of health care services during 12 months of follow-up
3. To study whether efficacy of CGC on mobility, p-and i-ADL and cognition were dependent of age, gender, pre-fracture function and type of fracture in the two groups (Paper III).

*) Results from cost- and health economic analysis are covered more thoroughly in another thesis by Gunhild Hagen.

3. Methods

The Trondheim Hip Fracture Trial was a parallel group RCT. The trial was planned according to CONSORT-criteria for RCTs.(246-248)

3.1 Study design

3.1.1 Planning of the study

The planning process was in principal divided into two separate parts and took place autumn 2007 and spring 2008. The core research group involved researchers experienced in planning and conducting large clinical trials, with scientific competences both in geriatric medicine, orthopaedics, health economics, and gait and falls research. We also engaged international capacities in clinical research and statistics. Locally, the research group collaborated with the Unit of Applied Clinical Research at the NTNU on data management and a web-based, computer-generated randomization service. At a later stage health economists and statisticians from NTNU were involved.

The summer 2007 an application for funding was submitted to the Norwegian Research Council, later offering a grant which only partly covered running costs and salaries. Agreement was signed in January 2008. Complete funding was received at a later stage with funds from The Central Norway Health Authority; The Department of Neuroscience, NTNU; The St Olav Trust; the SINTEF and St Olav Fund for Science and Innovation and also the Municipality of Trondheim. The study protocol was approved by the Central Norway Ethics Committee by spring 2008, and the study was registered in ClinicalTrials.gov in April 2008. The original study protocol was published as a journal paper in 2011.(219)

A parallel process focused at the clinical care pathway that was developed based on previous routines in the geriatric ward for comprehensive geriatric assessment and management, a literature review on evidence for treatment of hip fracture patients, visiting Diakonhjemmet hospital in Oslo, and teaching from the Departments of orthopaedics and anesthesiology. The assessment and treatment program was continuously adjusted to changes in Best Clinical Practice during the study, and was published as a separate paper (Paper I) after finishing the enrollment period.(249)

3.1.2 Randomized controlled trial

The design chosen for the study was a prospectively randomized parallel group design. After the orthopedic surgeon on call had diagnosed a proximal hip fracture and found the patient to be eligible, the nurse in charge of the patient asked her or him to participate, and collected a written informed consent. After the patients had given their informed consent they were randomized by the same nurse in the Emergency Room. If a patient was unable to give consent, for instance due to acute delirium, written or oral consent from next of kin were collected. Whenever possible, a regular consent was collected from the patient retrospectively. If next of kin was unavailable, the Regional Committee of Ethics in Medical Research allowed patients unable to give informed consent to be included as it was considered unlikely that CGC would harm the patient as compared to standard care, but a written consent had to be collected retrospectively.

The scientific staff controlled the admission list for the Department of Orthopedics every day to identify hip fracture patients not randomized in the Emergency Room. These patients were included and randomized up to 24 hours after admission or until receiving surgery using the same procedure as in the Emergency Room. Patients already operated and returned to OC were not included. Patients allocated to CGC were either transferred immediately or stayed in OC until surgery and transferred to the geriatric ward immediately afterwards.

We used a web-based computer-generated randomization system prepared by the Unit of Applied Clinical Research, NTNU. The participants were randomised in a 1:1 ratio with blocks of unknown size. After randomization the patients

were transferred to their allocated ward. Except for surgery, all patient treatment would be delivered in the allocated ward.

Patients not eligible or not willing to participate in the study were registered with initials, gender and date of birth and reason for ineligibility.

3.1.2.1 Study related assessments

Patients were assessed at the 5th postoperative day (± 1 day), at 1 month (±1 week), 4 (±2 weeks) and 12 months (±1 month). Some patients not able to attend a scheduled appointment (for instance due to travel or disease) were assessed per telephone.

3.1.3 Blinding

It was considered impossible to blind participants and staff including surgeons for patient allocation. It was also impossible to blind assessors the 5th postoperative day when assessing patients at the hospital ward. Even if assessors did not receive any information of allocation, assessments during follow-up were only partly blinded as they might remember the patient from the index stay. In order to check if this influenced the final scores we controlled if scores deviated when assessors were the same at index stay and follow-up as compared to different assessors.

3.2 Study population

The St. Olav University Hospital serves the county of Sør-Trøndelag with a population of 290 000 inhabitants in 2008. The population is relatively homogeneous mainly consisting of Caucasians. Approximately 1/3 of the population is served by a community hospital in Orkdal and was not eligible for the trial. At the study start we selected participants from four municipalities; Trondheim, Melhus, Klæbu and Malvik with 179000, 15000, 6000 and 13000 inhabitants, respectively. These municipalities were chosen because they were in close proximity with the hospital, and would give a mix of urban- and rural population. The proximity with the hospital was considered important to achieve a high participation at follow-up and to diminish the patient stress of having to go to the hospital. The area of recruitment was extended to the entire county after some months due to slow recruitment rate and difficulties for the emergency staff to comply with these criteria.

Patients were eligible for participation if they were 70 years or older, home-dwelling and able to walk at least 10 m. They were ineligible if they had a pathological fracture (due to cancer), late-stage malignant disease, other disease with an expected survival of less than 3 months, had suffered a high-energy trauma or were already included in the study.(219)

3.3 Delivery of patient treatment

Detailed checklists, assessment procedures and delivery of treatment are presented in Paper I.(249) This paper presents treatment in the experimental and the control groups and gives information on similarities and discrepancies between the treatment arms.

3.3.1 Facilities

The St. Olav University Hospital is a modern university hospital with a wide range of facilities. It is the community hospital for Trondheim and surrounding municipalities. It is also a tertiary university hospital for the three counties Sør-Trøndelag, Nord-Trøndelag and Møre & Romsdal. During the study the entire hospital was renewed and the building process was finished in 2013. The geriatric ward had been transferred to new facilities at study start and consisted of 15 single bed rooms organized in two bed clusters connected to a work station. Five beds for hip fracture patients were gathered in one cluster with a total of seven beds. In periods of high activity, the remaining two beds

were used for hip fracture patients as well. In periods of low activity, the fracture beds were used by patients suffering from other fragility fractures or acute geriatric conditions.

The ward was constructed to facilitate orientation in older persons with light colors of walls with clear contrasts in doors or other obstacles, good lighting in rooms and hallways. The environment was enriched with clocks and calendars in every room to support orientation. Patients had access to papers, and there was radio, television and internet access in each patient room. The ward had one dining room, and patients were in general encouraged to have their meals in the dining room to get social stimulation and as part of mobilization. The ward had wide corridors and there was abundant space for walking with any aids and thereby stimulating mobilization.

At study start the orthopedic ward was located in the old part of the hospital with two- or four bed rooms in light colors without any elements specially added to facilitate orientation. Meals were served in the patient rooms. September 1st 2009, the orthopedic ward was moved to a new center with wards that were equivalent to the geriatric ward.

3.3.2 Standard treatment in the groups

Regardless of treatment allocation, all patients were admitted to the Emergency Room and examined by the junior orthopedic surgeons on call. Surgery was performed by the orthopedic team on call, a junior surgeon on call with adequate experience in trauma surgery or the senior surgeon if considered necessary. Similarities in treatment are shown in Paper I, table 3. All patients received intravenous fluid at arrival, anti- thrombotic prophylaxis, paracetamol and femoral nerve block as baseline pain treatment and prophylactic antibiotics related to the surgery in most cases. Early removal of urine catheter and focus on prevention of pressure ulcers were standard in both arms. All patients had access to physical therapy.

There was no difference between groups with respect to choice of surgery which was decided by the operating surgeon using recommendations as described in Chapter 1.2. Before surgery all patients were examined by the anesthesiologist on call who evaluated if the patient was fit for surgery and the choice of anesthetic method. Almost all patients received spinal anesthesia. In the CGC arm patients were also examined by the medical resident on call between 1600 and 0800 and during weekends, and by a geriatric resident/consultant between 0800 and 1600. If indicated, the geriatric/medical doctor would discuss per operative risk with surgeon or anesthesiologist, for instance the risk of arthroplasty in patients who were unlikely to tolerate low blood pressure during installation of cement. Occasionally surgery was postponed until the patient was deemed sufficiently fit.

3.3.3 The intervention arm (experimental)

The main element in the intervention was comprehensive geriatric care (CGC). This method is summarized in Table 2, Paper I. It consists of a multidimensional assessment of somatic and mental health, general function and social situation. The evaluation was performed by an interdisciplinary team consisting of a consultant or resident in geriatric medicine, nurses, a physical therapist, an occupational therapist. Other medical specialists were requested when indicated. Each team member had dedicated responsibilities. The team used established and validated tests for individualized treatment planning including an early plan for discharge and necessary follow-up. We had a defined intention to discharge patients directly to their own home without institutionalized rehabilitation if possible.(244) We did not establish any strict criteria for this, but the decision was made at the interdisciplinary team meeting in understanding with the patient and her next of kind, and the municipality. Early discharge planning was emphasized including if patients needed extra care or aids after returning home. To facilitate discharge to own home, patients were introduced to this concept at an early stage of rehabilitation. Patients received written information at discharge to own home. If discharged to an institution they received only oral information to avoid later confusion in respect of

drug regimen or treatment plans, while the responsible institution received a full medical report including lists of drugs and instructions for further treatment.

Differences of treatments are summarized in Table 3, Paper 1. The number of staff per bed is higher in the CGC than the OC and includes more nurses (1.67 and 1.48), more doctors (0.13 and 0.11) more physical therapists (0.13 and 0.11) and occupational therapists (0.13 versus none). Physical and occupational therapists in CGC were integrated in the ward, and were involved as a routine practice with the patient from admission without referrals. There was a more vigorous follow-up of fluid intake and nutrition, assessment of pain by the use of a verbal rating scale and focus on adequate treatment of pain in the experimental group.(250) Delirium was evaluated using CAM. If saturation was below 95 percent, extra oxygen was administered with nasal catheter or mask. Blood transfusion was given with an HgB <10.(152) Patients were screened for constipation and urinary retention. Laxatives were administered prophylactically in nearly all patients. Among cognitively impaired patients frequency and amount of defecation was registered and necessary actions taken if there were signs of constipation. Patients were screened for urinary tract infections by using urinary sticks at admission and by withdrawals of catheters, and urinary retention by using a bladder scan. Intermittent catheterization was performed if signs of urinary retention. Most patients in the experimental group were screened for osteoporosis either during the hospital stay or were referred to such screening after discharge. If untreated before and expected to live long enough to benefit, treatment with calcium and/or bisphosphonates should be initiated during the hospital stay, in the out-patient clinic of the Department of Endocrinology or by the general practitioner.

Early mobilization was an essential part of CGC. If possible all participants were therefore mobilized the 1st postoperative day by a physical therapist and a nurse, and a plan for the mobilization of each patients was made based on pre-fracture function and the current medical situation. The ward was designed to facilitate mobility as described under facilities. The physical therapist participated in mobilization of all patients and supervised the staff in mobilization methods. However, she had her main focus on patients with the most challenging mobility problems while other patients were encouraged to ambulate and were assisted by other staff members to ensure activity. Supportive equipment as walkers and rollers was always available in the ward. The occupational therapist ordered the correct aid at discharge, and the appropriate aid was present when returning home or in a rehabilitation facility. The Cumulated Ambulation Score (CAS) was used the first three days after surgery to assess mobility.(251)

The drug regimens were evaluated for all patients. Before surgery we identified drugs considered unnecessary or potentially harmful that should be discontinued permanently or temporarily in relation to the surgery. ACE-inhibitors and diuretics given against hypertension were generally stopped. Drugs that should be administered before surgery were specified (for instance beta-blockers in patients with known cardiovascular disease), either orally if possible, or as injections. Extra steroids were administered in patients with possible adrenal insufficiency (mainly due to corticoid treatment). A specific focus was given to anticoagulants (vitamin-K antagonists) and novel anti-platelet drugs (for instance clopidogrel). For vitamin K-antagonists we considered INR level which should be below 1.8 in case of spinal anesthesia. This was achieved by drug cessation and/or administration of K-vitamin. In some cases coagulation factors were administered intravenously. For potent platelet inhibitors surgery was postponed or platelets were transfused (due to the risk of spinal hematoma) depending mainly on the choice of the anesthesiologist.

After surgery a comprehensive evaluation of the drug regimen with respect to indication for treatment, doses, possible side-effects and under-treatment of medical conditions was performed. There was a specific focus on drugs associated with falls such as CNS-acting drugs including sedatives, and drugs affecting the cardiovascular system. A special attention was given to drugs with potential anticholinergic side effects. The START and STOP criteria were applied to a certain extent, although not systematically.(252) In patients using diuretics the diuretic was removed if

the treatment indication was weak or absent, or if the patients suffered from side-effects as orthostatic hypotension and/or urinary incontinence. If indicated, patients with long-lasting anxiety or depression could be offered specific treatment of their disorders if considered potentially beneficial. In most cases, however, this decision was left for the patient's general practitioner (GP) as a post acute surgical setting is not optimal for a correct diagnosis. Cognitive impairment was common, but in a postoperative setting it would not be appropriate to diagnose dementia and therefore treatment with cholinesterase inhibitors was not started during the hospital stay. If indicated, the patient's GP was recommended to initiate evaluation of tentative cognitive impairment and depression when the clinical condition had stabilized after the trauma (i.e. 3 months).

3.3.4 Traditional orthopedic Care (Control)

The orthopedic ward followed standards of orthopedic care in Norway. Patients were evaluated in traditional ward rounds with nurse and surgeon and being mobilized the 1st postoperative day. Meals were served in the patient´s room. All patients were formally referred to physical therapy if not considered unfit. Pain medication was administered as baseline paracetamol and long- or short-acting opioids if indicated. There was no systematic review of patient drugs during hospital treatment (the routine for vitamin-K antagonists and platelet inhibitors were similar as for the intervention), and during the study period no clinical pharmacologist was employed at the department. A comparison of treatment in the geriatric intervention ward and orthopedic ward is given in table 3, Paper I.

There was no structured and team-based discharge planning, but discharge was ordered by the responsible surgeon. The patients received information from the surgeon, responsible nurse and physiotherapist if indicated. As for the intervention, patients only received written information when discharged to own home. The patient's GP and institutions receiving the patient after discharge received a written report as standard.

September 1st 2009 the orthopedic ward changed facilities from the old ward with two- and four-bed rooms, to a new building with single-bed rooms with modern facilities. At that time 219 of 397 patients had been included in the study.

3.4 Outcomes

The Trondheim Hip Fracture Trial has used a variety of different outcome measures.(219) Most of our tools are validated for the group studied and are recommended for use in frail populations. Performance based tools are used when available and eligible, and especially for the primary outcome, while e interviews with patient or caregiver are used if appropriate for some secondary outcomes. This section contains a presentation of each outcome and a summary of each tool describing:

- Measured outcome, and associated tests
- Description of the different elements of the test
- Strengths and weaknesses
- Definitions of clinically important change

3.4.1 Mobility

Mobility at 4 months was the primary outcome. Both assessment instruments were performance based and testing lower extremities function.

3.4.1.1 Short Physical Performance Battery (SPPB)

SPPB has three domains: Balance (0-4 points), sit to stand (0-4 points) and gait speed (0-4 points) scoring a total of 12 points.(253) It is found appropriate in frail and old populations. It has a ceiling effect in very healthy and mobile

individuals, but in a hip-fracture population this is not a problem. The possibility of a nil score for patients unable to walk prevents a floor effect.(254) A change in scores of 0.5 points for the individual patient is found to be clinically meaningful, while a difference of 1 point is substantial.(255)

3.4.1.2 Timed Up and Go (TUG)

TUG measures time used for a patient sitting on a chair to stand up, walk 3 meters, turning, and walk back and sit down again.(256)The main strength of the method is its widespread use in studies of old in general and in hip fracture studies. The main weakness is a pronounced floor effect as many patients are unable to get a score if unable to walk, and it does not discriminate between different difficulties of walking (for instance difficulties in standing up from a chair as compared to slow walking speed).

There are no studies evaluating clinical meaningfulness of changes in TUG scores.(257) There are, however, data on normal scores and scores associated with adverse outcomes as falls. In a healthy population a normal score is less than 10 seconds, while spending more time than 16 seconds is associated with increased risk of falling.(258, 259)In hip fracture populations, a TUG score >24 seconds is associated with increased risk of falling after discharge from hospital.(260)

3.4.2 Activities of daily living (ADL)

3.4.2.1 Barthel Index (BI)

BI is a measurement of p-ADL.(261) It is a 10 item questionnaire with a maximum score of 20. The items of BI are feeding (0-2 points), bathing (0-1 points), personal hygiene (0-2 points), dressing (0-2 points), bowel control (0-2 points), bladder control (0-2 points), use of toilet (0-2 points), transfer between chair and bed (0-3 points), mobility (0-3 points) and stair walking (0-2 points). Maximum score of each item is 1 to 3 points.

An advantage of BI is that it is well established and widely used both in clinical practice and research. It may be used both as a questionnaire or in interview both face to face or by telephone and still have acceptable precision.(262) BI is found to have an acceptable sensitivity to change that is valuable in a longitudinal study, but it may have a floor effect in very frail populations and a ceiling effect in populations with better functional capacity.(263)

Depending of methods used, Minimal Clinical Important Difference (MCID) is between 1.49 to 1.85 points. (264)Impairment in BI would be a strong indicator of dependency, increased LOS and in many cases indicates need for 24 hours care or at least need for rehabilitation.(265)

3.4.2.2 Nottingham Extended Activities of Daily Living (NEAS)

NEAS is a measurement of i-ADL. It was developed primarily as a measurement of i-ADL in stroke patients,(266) but has previously been used in hip fracture and hip replacement populations.(42, 267) It consists of four domains with 22 items scoring 0 to 3 points giving a maximal score of 66: Mobility with six items: outdoor walking, stair walking, getting in- and out of a car, walking on uneven ground, ability to cross roads and use of public transport. Kitchen activities with five items: independent feeding, ability to make a hot drink, ability to transport a hot drink between two rooms, dishwashing and cocking a meal. Domestics with five items: managing own money, hand-washing of clothes, housework, shopping and laundry. Leisure time activities with six items: Reading books or papers, use of telephone, writing letters, going out socially, gardening and driving.

It is used in hip fracture studies,(268), but is less sensitive to change in a healthier population (osteoarthritis patients).(269) It has no obvious floor effects, while a ceiling effect has been observed in high functioning hip replacement patients.(267)

In stroke populations, MCID is found to be between 2.4 up to 6.1 points making differences within this interval likely to be relevant and higher values certainly relevant.(270) Specific data for hip fracture patients have not been found.

3.4.3 Cognition

Cognitive function can be tested with performance-based methods, and with questionnaires. Tests by questionnaires are necessary to gain any pre-fracture data. We have therefore used both methods.

3.4.3.1 Clinical Dementia Rating (CDR)

CDR is an established questionnaire-based method to evaluate cognitive function. (271) It has been used to screen for dementia since 1982. It consists of six domains; memory, orientation, judgment, community affairs, home and hobbies and personal care. Each item scores 0=normal; 0.5= slightly reduced; 1= mild cognitive failure; 2=moderate cognitive failure and 3= severe cognitive failure. We have used the sum-of-boxes approach for scoring, where the scores of each item are summarized into a total score which is used to categorize the patient into four categories; normal (0 points), possibly reduced (0.5 to 4 points), mild dementia;(4.5 to 9.5 points), moderate dementia (10-15.5 points) and severe dementia (16 to 18 points.(272)

CDR allows for all sources of information to be used in scoring the patient even if it is primarily designed for carers and next of kin(273) It allows for information to be collected in retrospect,(274) making a pre-fracture estimation of cognitive function possible. It has a strong focus on memory (in the original test by Hughes it was the main category, with the five other categories used as adjustment) making it primarily a test for Alzheimer's disease and not the more general group with cognitive impairment. It is not sensitive to change, and we have not found any data on MCID even if the sum-of boxes approach may make such analyses more feasible than the standard approach.(272) The Washington University Alzheimer's Disease Research Centre who created the test recommends that users take an online seminar to ensure reliability of scoring.

3.4.3.2 Mini Mental Status Examination (MMSE)

The MMSE is an extensively used performance based screening test for cognitive impairment.(275) It is designed for repeated testing with specified instructions when retesting the patients. Time between tests affects reliability, and test intervals of less than six months have an uncertain value. (276) MMSE consists of 20 items in five groups; orientation (10 items 10 points), registration (1 item 3 points), calculations and attention (1 item 5 points), recall (1 item 3points) and higher functions (language and constructional praxis; 7 items 9 points).(277) The maximum score is 30 points. Traditionally between 24 and 30 points was considered normal, mild cognitive impairment from 22-24 and dementia below 22 points, but most clinicians treat these thresholds with caution as they are influenced by educational level and age. A person with an academic degree or profession are likely to score better in an early stage of dementia, and a candidate with only primary school or less may have a normal cognitive function with a score of 22.(277)

It has a better sensitivity to change than the CDR, but it is not very sensitive.(276) A change in MMSE of 2-3 points is considered to be of importance.(277)

3.4.4 Mood

3.4.4.1 Geriatric Depression Scale (GDS)

GDS short-form with 15 questions was used to evaluate depression in our study.(278) This is a generic questionnaire with a dichotomous yes/no option developed for an old population, and it has also been used in hip fracture studies.(279-281) GDS has a factor structure of five groups within the domains; sad mood, lack of energy, positive mood, agitation and withdrawal.(282) Each of the answers indicating depressive symptoms is scored one point. There

is a cut-off for probable depression at 7 points. It may be less sensitive for depression in institutionalized patients,(283) and there is conflicting evidence regarding sensitivity to change.(284, 285)

3.4.5 Fear of falling

3.4.5.1 Falls Efficacy Scale International –short (FESI-s)

We have used the FESI-s to assess fear of falling. (286) This is a 7-item scale based upon the original 16 item FESI developed by the Prevention of Falls Network Europe (ProFaNE).(287) The seven items are: dressing or undressing- taking a bath- getting in or out of a chair- walking stairs- reaching for something above your head or on the floor- walking a slope- participating in a social event. Each item may be scored 1-4 points, spending from: Not at all concerned to very much concern with possible sum scores from 7 to 28. Compared with the original FESI, it is easier to perform and less exhausting for frail patients. The short-FESI has showed good validity regardless of cognitive function.(288) When used in populations with risk of falls or recent falls it has no ceiling effect, and there is no floor effect in frail populations.(289)

It is found to be reasonable sensitive to change.(288) Trials have identified cut-off values correlating with low (7-8 points), moderate (9-13) and high risk (14-28) of falling for FESI-s.(289)

3.4.6 Quality of life (QoL)

Tools for estimating QoL may be disease specific or without connection to the disease studied.(290) The latter instruments are necessary to perform cost-utility analysis.

3.4.6.1 EuroQol

EuroQol is one of the most widely used generic instruments to estimate QoL.(291) We have used the EuroQol 5 dimensions (EQ-5d) instead of the original with six dimensions .(292) The five domains are mobility, self-care, usual activities, pain/discomfort and anxiety/depression and each item scoring from 1 to 3, no problem to unable to perform or maximal problem. This generates a 5-digit code between 11111 (no problem in any field) and 33333 (worst quality of life imaginable). Each combination of digits gets a decimal value between -0.594 (worst possible quality of life and 1 (perfect life). Death has a defined score of 0 indicating that some states are considered worse than death.

A separate part of the instrument is the EQ-5d scale ("thermometer") scoring between 0 and 100 were 100 is perfect health, whereby the patients score their health on a VAS scale between 0 and 100.

3.4.6.2 QALYs (Quality adjusted life years)

QALYs are used in cost-utility analyses. The general expression for QALYS can be written as follows:

$$QALY = \sum_{t=0}^{n} \left[\frac{(Q_1 + Q_{t+1})}{2} \times \frac{T_{t+1} - T_t}{T} \right]$$

The numbers of measurements are n, T is the time of the study period and Q is the utility measurement. Q_t is the utility value at time t. (293)

QALYS are calculated from the difference in a generic utility value, for instance EQ5-d over a given period of time. One QALY equals one year in perfect health.(294) A treatment improving the EQ-5d score with 0.1 point over one year gives a benefit of 0.1 QALY. If the extra cost of the treatment is 5000€, the cost utility result will be 50000€/QALY. As cost utility analyses are not a part of this thesis, this will not be discussed any further.

3.4.7 Baseline registrations

3.4.7.1APACHE II

The APACHE-II is a system to evaluate and estimate preoperative risk. (295) It is a complex algorithm containing a series of clinical variables as well as information of chronic and acute disease. This generates a score that gives an estimate of risk related to surgery. It consists of 12 physiological measurements: Temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, pH, s-sodium, s-potassium, s-creatinine, hematocrit, white blood count and Glasgow Coma Scale (GCS). We calculated hematocrit from hemoglobin and did not measure hematocrit separately.(296) Each measurement is given a score from 0 (normal) to 4 (highly abnormal- low or high). The APACHE II score is the sum of A+B+C.The sum of values of the physiological score generates value A. Value B is deduced from the patient age; <44 years 0 points; 45-54 2 points; 55 to64 3 points; 65-75 5 points and >75 6 points. Chronic diseases are scored under C and give 5 points for emergencies or non-surgical patients (for instance a septic infection) having terminal liver, lung, renal or heart failure or immunodeficiency (related to drugs or disease). Elective surgical patients get 2 points for the same disorders. In our study minimum APACHE II score is 5 due to age.

We assumed that missing physiological variables were normal if not registered at admission. GCS, heart rate and blood pressure were in general well documented, while respiratory frequency was occasionally missing. To affect APACHE II it had to be above 25. Earlier studies have shown that approximately 35% of patients have minor abnormalities at admission, but most of these were laboratory anomalies that were routinely done in the ER in our study and few patients had deviations in physiological variables. (297)

3.4.7.2Charlson Index

Charlson index of comorbidities consists of 17 different diagnostic groups scoring from 1 to 6 points.(298) Diagnosis of cardiac infarction, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, pulmonary disease, connective tissue disease, peptic ulcer, liver disease and diabetes scores 1 point. Complicated diabetes, paraplegia, renal disease and cancer scores 2 points. Metastatic cancer and severe liver disease scores 3 points and HIV-infection scores 6 points. Only diseases identified at admission were used.

3.4.7.3 Type of fracture

All fractures included in the study were coded according to the ICD10 as proximal femoral fractures. The fractures included are femoral neck (S72.0), per- trochanteric (S72.1) and sub-trochanter fractures (S72.2). The fractures are registered both with their respective code, and collapsed and dichotomized as intra-capsular fractures (S72.0) or extra-capsular fractures (s72.1 and S72.2).

3.4.7.4 Surgical procedures

There is a variety of surgical procedures available for hip fracture patients. We have registered surgical codes as specified in the surgical description, and we use The Nordic Medico-Statistical Committee Classification of Surgical Procedures (NCSP) for coding. All codes are in Chapter N for movement apparatus and F for proximal femur. In the analyses we have not differentiated between hemi-arthroplasty and total arthroplasty as very few patients were offered the latter alternative.

When presenting data in regard of procedures, we have collapsed surgical codes into four groups: arthroplasty, screws, plates and other. Even in the collapsed form, patients may have more than one procedure.

3.4.7. 5 Other

We registered, if available, demographic characteristics of marital status (married, widowed), living arrangements as living alone or with family members (co-habitants) and residing in sheltered housing. Prescribed drugs and regular use of prescription free drugs such as NSAIDS or paracetamol were also registered.

3.4.8 Clinical registrations

Clinical variables were registered manually by extraction from medical records including notes, charts, surgery, forms, imaging reports and laboratory data.

3.4.8.1Complications

We have registered a number of complications during the index stay. We had a specific focus on infections, especially urinary- , pneumonia and wound infections. We also registered other major complications as they were documented in the patient´s medical records: heart attack, stroke, surgical complications, thromboembolic complications as deep venous thrombosis or pulmonary embolus and complications due to failure of an arthroplasty. For identifying infections we used notes in medical records or start of antibiotics indicating an infection if information in medical notes were lacking. Delirium was not registered as part of the study, even if it was identified as part of the clinical treatment program in the CGC arm.

To identify bleeding we have used notes in medical records in combination with information of transfusion. We have registered information of transfusion pre, per- and postoperatively including number of units of blood or erythrocytes administered.

Serious complications after discharge may lead to readmissions, but a majority of readmissions are for non-surgical complications which are difficult to differentiate from new disease.(299) Readmissions are therefore described in 3.4.9.

3.4.8.2 Mortality

Data on mortality are registered one year after fracture. Date of death is collected from The National Registry. The last registration of death was made January 2012 as the finally enrolled patient finished one year follow-up. We therefore possess complete data of death during follow up. Data of death is presented as death before surgery, one month, four months and as 12 months mortality. We have not specified in-hospital mortality.

3.4.9 Use of health care services

We have registered use of health care services during one year after the fracture. The registration includes use of both in-hospital resources and use of services in the municipalities. Data from the index stay and readmissions were collected from National Patient Registry (NPR) and hospital registries, while data from the municipalities were collected from The National Registry for Statistics of Individual Care and Nursing (IPLOS). Data were registered one year after the initial admission.

NPR delivered data on LOS and readmissions based on a patient file with identifiable data including date of birth and admission. Data form the municipalities were collected in two ways. A research assistant (physiotherapist) was granted access to the registries of the municipality of Trondheim and registered the available data directly in the database. For the remaining municipalities, forms for the individual participant was sent and filled in by staff in the municipality. The forms were then returned and registered in the database by a secretary at the Department of Geriatrics.

All services that include a stay at a treatment facility are registered as LOS in hospital, rehabilitation and nursing home care. A patient is registered as admitted the day she arrives regardless of time of the day until and including the day of discharge. When use of resources overlap (for instance at discharge between two levels of care), the highest level take precedence.

3.4.9.1 In-hospital use of health services

In-hospital resources include facilities, personnel resources and consumer goods used by the individual patient. Table 1, Paper I gives an overview of type of resources used in each arm of the study. Personnel resources are defined as staff per bed and are a constant for each ward. The number of staff per bed is higher in the CGC than the OC as described under Methods section 3.3.3. Facilities are described in Methods section 3.3.1.LOS times the constant for each ward is the actual use of health services within the ward. Consumer goods consists mainly of resources used during surgery, and is not discussed any further in this thesis as it is independent of allocation as defined by randomization.

3.4.9.2 Rehabilitation

We registered rehabilitation as LOS in a rehabilitation facility. This includes rehabilitation as registered in NPR in specialized rehabilitation facilities (similar to in-hospital rehabilitation), District Medical Centers which are inter-municipal rehabilitation facilities and rehabilitation wards (similar to a skilled nursing facility) in single municipalities often located in a nursing home. These data were collapsed before final analyses into one group.

3.4.9.3 Use of health services in the municipalities

Care provided by the municipalities is registered in for all patients receiving any form of care. We have also used data from NPR for medical consultations and for consultations with PT paid over NPR. We have not registered informal care or care provided by private suppliers.

Table A2 (appendix paper 2) gives a detailed list of services including nursing homes. Services are listed dichotomized (have/have not) or as a volume with an appropriate measure (days, hours, minutes). Data of start and stop of a service is also registered. Services are registered as intended use (decision), not as actual use.

3.5 Statistics

In addition to a description of the methods used to analyze data in a study, statistics also includes a comprehensive description of handling of data including analysis, efforts to avoid missing data and the quality process in registration and controlling the data files. Transparency in data handling is important to achieve quality during the entire process. The principles used to handle data in our study are described in our analysis plan (Appendix).(300) Elements to ensure quality are patient relevant outcomes, realistic test schedules at follow-up, efforts to reduce participant attrition and finally a multi-level quality control system with independent and repeated controls of quality, evaluation of types of missing data, imputation when appropriate and use of robust pre-specified analytical methods to avoid "shopping for p-values".

3.5.1Types of data

Our data are in four groups, nominal data as type of fracture or choice of surgery, binomial data as gender or group allocation, discrete variables as the SPPB, FESI-score or number of drugs and finally continuous data as TUG-score in seconds, age or LOS. Due to the size of the scales of the discrete data, they are treated analytically as continuous data.(301)

Most data in our study are repeated measurements allowing for use of methods for longitudinal analysis. Data from the index stay and background data are measured once and analyzed by methods appropriate for single measurements.

3.5.1.1 Distribution

Most outcomes are normally or close to normally distributed. Most baseline data are binomially distributed. Distribution is checked for by manually inspecting distribution curves and Q-Q plots

3.5.2 Missing data

Missing data is a challenge in all clinical trials, but especially important in studies of frail elderly persons.(302) Missing data may be due to attrition, mortality, intercurrent disease or missing attendance due to other causes. Predefined strategies on how to handle different types of missing data, and systems for evaluation of missing data is important.

We can divide missing data in three categories, missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR).(303) MCAR is in principle completely independent of outcome and subject tested and happens by chance alone. MAR exist if "the probability of dropout is conditionally independent of the unobserved measurements given the observed measurement" or that no confounder may explain the missing data, only the information already present.(304) MNAR has a clear correlation between missing data and a factor with the subject. An example of MCAR is loss of data due to a technical error with equipment while an example of MAR may be a patient failing to attend a test due to intercurrent disease (related to decline of health).In MNAR there is a correlation between the missing data and the patient. For instance, when comparing to regimes of cancer treatment, one regimen may have more missing data due to more side effects than the other regimen.

3.5.2.1 Type and handling of missing data

In our study the following categories of missing data was identified and handled as described. We have analyzed all data as intention to treat (ITT) including patients with missing data or incomplete follow-up in the analyses.

Missing items are the most common kind of missing data. In our study missing items were present, but to a moderate degree (<5%). We used simple imputation by the Expectation Maximation (EM) algorithm for imputation of single and double missing items on questionnaires and performance tests, using scores from the same time-point as predictors. (304) If the algorithm created an impossible value, the result was corrected to the closest possible value for the actual item. Imputed values including a decimal number were used even if the regular items only included integers. Multiple imputation were used to a limited extent in our study.(305) In paper II, multiple imputation was used on EQ-5d as a part of the cost utility analysis.

Missing forms are not unusual, and at each scheduled appointment 10% of participants had one or more missing forms. This could be related to patients being unable to attend, but still being able to answer some of the questionnaires for instance by telephone. Forms with >2 missing items were considered missing. Missing forms are handled by mixed models which are a way of reducing the consequence of missing data in longitudinal studies. It uses available data, and does not need complete datasets to do an analysis.(306) It is sensitive to NMAR and a careful evaluation of the cause of missing data should be performed before using mixed models.(307)

Missed appointments were registered to a limited degree and are presented in the flow chart, Paper II. We have differentiated missing appointments due to absence and death were the data is not missing, but do not exist (except for EQ-5d with a score of zero). As for missing forms, missing appointments are handled by mixed models.

To reduce the risk of absence, extensive measures were taken. Participants received written information of when to meet in advance of every visit to hospital for assessments. The day before tests, patients were reminded of the appointment by phone. Patients from the municipality of Trondheim were transported to the hospital by a dedicated taxi driver who assisted the patients from house to the test lab and back. The same driver was used during the entire project to increase comfort and feeling of safety for the patients.

3.5.2.2 Withdrawn

Participation in the study was voluntary and some patients withdrew. Most patients withdrew from further assessments, but accepted that data was collected from registries, only one patient refused both further assessments and collection of any data from registries.

3.5.3 Data analyses with mixed models

All analyses of repeated measurements in our study were done by longitudinal mixed models. This method has several advantages. It is considered the preferred method when there are missing data, when the pattern of missing is CMAR or MAR, when the study population is large or moderately large, and when data is collected over time with irregular time intervals.(307) Mixed models are in general more robust to violation of assumptions as compared to other methods of analyzing longitudinal data.(308)

The analyses in our datasets are done on total scores for each test at each time point. We have performed simple imputation as described above to increase precision of our estimates, and to use as much of available information as possible. Outcomes are dependent variables, with time and group allocations as factors.

3.5.3.1 Co-variates

A key element of mixed models is to increase precision of the analysis by using co-variates as a controlling element.(308) This reduces errors and standard deviations. We have chosen our covariates in this study based on clinical judgment because the selected covariates are likely to be of importance. In the present papers, gender, age and fracture type are covariates as all are shown to affect outcome.(92, 309)

3.5.3.2 Interaction analyses

An interaction analysis are a mixed model were additional factors are added to the analyses, evaluating the effect of each factor of the total effect and if the factor significantly affect outcome. In paper III we present 16 two-way interaction analyses where age, gender fracture-type and function by NEAS are used as factors when analyzing SPPB, BI, NEAS and MMSE.

3.5.3.3 Sensitivity analyses

Sensitivity analyses are used to evaluate if a change in assumptions affect a result of an analysis. An example is to perform analyses of both intention to treat and per protocol analysis to see if conclusions differ, or perform analysis with and without outliers in a dataset. It is customary to use the same methodology in a sensitivity analysis as in the regular analysis. We have used two-way interaction analyses in mixed models with treatment in old orthopedic ward as a dichotomized factor. The analysis was performed for SPPB, BI and NEAS.

3.5.4 Other analysis

Most analyses in this study are mixed models on longitudinal data. However, some data from the index stay and also background data are not longitudinal. We have used linear regression to evaluate LOS during the index stay. We wanted to use similar methods including the same co-factors as were used in mixed models, but without longitudinal data.(301) Chi- square tests were used to compare groups in cross tabulations of baseline values. We have used the methodology developed by Newcombe to compare proportions and create confidence intervals for proportions in the study.(310) The results from Newcombe`s test for differences between proportions are presented together with chi-square analysis.

4. Ethics

Research in humans is regulated by national laws in line with the Helsinki Declaration. (311, 312) All research on humans has to be approved by the Regional Committee of Ethics in Medical Research before collecting any data. Participation in research on humans is voluntarily, and written informed consent is in general mandatory. In cases where written informed consent is impossible (for instance due to reduced consciousness), consent has to be given by next of kin or a legal guardian. When patients are not legally competent (for instance children, patients with

severe mental disorder or dementia), permission to participate are given by their legal guardian. The patient might still refuse to participate. The research should be possibly beneficial for the patient, and it should be terminated immediately if the method investigated is proven inferior to standard care. The research should also be stopped if the novel method during the study is proven superior. The Regional Committee of Ethics in Medical Research is responsible for other permissions related to the research as permission to create a bio-bank or applications for the Norwegian Data Protection Authority. Human Research in Norway is by law open for inspection by the Regulatory Authority and this includes access to data.

This study was approved by the Regional Committee of Ethics in Medical Research (REK4.2008.335), the Norwegian Social Science Data Services (NSD19109) and the Norwegian Directorate of Health (08/5814).It was registered at ClinicalTrials.Gov with registry number NCT00667914.

4.1 Ethical considerations

Focus on evidence-based medicine has created a demand for evidence even for treatment of elderly, and methods to reduce the challenges for elderly recruited to research are wanted. Old patients are considered more vulnerable, and need extra protection in respect of research.(313) They may have changes in physiology making them more vulnerable for side-effects of treatment, they have more comorbidities including dementia and considerable proportions of patients are frail.(162) Complications, mortality and attrition increase risk of missing data.(314) Outcomes and tests should be validated both for the condition and for old patients.

As described in section 3.1.2 we collected written consent for our participants. If patients were unable to give their consent due cognitive impairment, we collected written consent from next of kin or oral consent from next of kin if they were not present on admission. When next of kin was unavailable, we had permission from the Regional Ethics Committee to include patients as the study was considered not to represent any extra risk for patients. In cases of lack of written consent or consent from next of kin we aimed at collecting written consent from the patient if he or she was able to give it later (for instance after a delirium).

5. Results and summary of papers

5.1 Paper I

Background: Hip fractures often have serious consequences on function, mobility and mortality. Studies have shown that interdisciplinary geriatric treatment may be beneficial compared to traditional treatment, and several models of orthogeriatric treatment have been developed.
Aim: Describe the theoretical basis of the model used in the Trondheim Hip Fracture Study and outline the treatment programs delivered in Department of Geriatrics and Department of Orthopedic Surgery (DOS), respectively.

Findings:
Basis for the experimental treatment:
Model: We performed a literature search exploring available orthogeriatric models and decided to evaluate a model with treatment within a geriatric ward with orthopedic consultations.

Comprehensive geriatric assessment (CGA):
CGA is shown to improve outcome in acutely sick elderly patients. It should be systematic and multidimensional. Treatment should be delivered in a dedicated unit. It should be based on protocols and assessment tools and focus on communication with caregivers and patients. Discharge planning should start as early as possible. Early mobilization and rehabilitation should be emphasized.

Developing a treatment program for hip fracture patients in a new clinical pathway:
The Department of Geriatrics (DG) had extensive experience in CGA on medical patients, but very limited experience in hip-fracture treatment. The new clinical pathway was based on previous routines of the DG, the existing peri-operative routines of DOS and the Department of Anesthesiology (DA) at our hospital and a literature review. As part of the development a group of clinicians visited the orthogeriatric ward at Diakonhjemmet Hospital in Oslo. The interdisciplinary team had input from DOS and DA through teaching and also visited the orthopedic trauma ward. The treatment program was piloted during four months before starting the study.
Program elements:

- *Patient flow:* Pre-and postoperative treatment were delivered in DG.
- *Organization of wards:* The orthogeriatric unit consisted of five beds that were added to the existing 10-bed geriatric unit. The team consisted of a medical doctor/geriatrician, nurse, physiotherapist and occupational therapist. The staffing per bed was higher in DG than in DOS.
- *Standard care:* Standard care was specified and according to national standards, including focus on hydration, femoral block as pain relief, prevention of pressure ulcers and early removal of urinary catheter.
- *Treatment in the experimental group:* Comprehensive geriatric care (CGC) should be based on an interdisciplinary multidimensional and systematic assessment of all patients focusing on each patient's capabilities and limitations as well as development of individual care plans. Discharge planning should start as early as possible similar to the approach used for geriatric patients without fractures.
- *Medical assessment and treatment:* The new program based on CGA included identification and treatment of comorbidities, pain relief, hydration, oxygenation, nutrition, elimination, prevention and management of delirium, assessment of falls and osteoporosis, and I early mobilization.

Discussion:
A new treatment program for hip fracture patients (CGC) was developed, introduced and run in the DG. The program is to be evaluated in an RCT with DOS as control.

5.2 Paper II

Background: Existing literature indicates that orthogeriatric interdisciplinary treatment of hip fracture patients is beneficial, but the evidence from large randomized clinical trials is limited. A promising model is the orthogeriatric unit managed by geriatricians with orthopaedic surgeons being consultants (except for the surgery).

Aim: to evaluate the effectiveness of comprehensive geriatric care (CGC) provided throughout the entire hospital stay as compared to standard care in orthopaedic trauma ward (OC).

Methods: The study was a prospective randomised clinical trial (RCT) with two parallel groups, but not blinded. Randomization was computer-based and performed in the emergency-room

We included home-dwelling patients 70 years or older and able to walk at least 10m. They should not suffer from a pathological fracture, have an expected survival shorter than three months and should not be the victims of high-energy trauma. The intervention took place during the entire hospital stay with no specific follow-up.

The primary outcome was mobility at four months measured by Short Physical Performance Battery (SPPB; 0-12, 12 better) , and the following secondary outcomes: mobility, p- and i-ADL, cognition, fear of falling, mood, quality of life, use of health care services and cost. Pre-fracture variables included personal activities of daily living (p-ADL) measured by Barthel Index (BI; 0-20, 20 better), instrumental activities of daily living (i-ADL) measured by Nottingham Extended ADL Scale (NEAS; 0-66, 66 better), cognition measured by Clinical Dementia rating (CDR; 0-18, 0 better) and early post-operative mobility measured by SPPB was collected at the 5th postoperative day. At one month mobility was assessed by SPPB and the Timed Up and Go (TUG; time in seconds). ADL was measured by BI and NEAS. Mini Mental Status Examination (MMSE; 0-30, 30 better) was performed for cognition, depression was evaluated by Geriatric Depression Scale (GDS; 0-15), fear of falling was investigated by Falls Efficacy Scale International (FESI; 7-28, 7 better) and quality of life was investigated by EuroQol –five dimensions (EQ-5d, -0.594-1, 1 better). The same test battery including CDR was used at four and 12 months. At 12 months we also collected data on use of health services from both the hospital and municipalities over one year after the fracture. In-hospital services included the index stay, readmissions and out-patient consultations, while use of institutions including rehabilitation facilities and nursing homes as well as home based services as home nursing, home care, safety patrol and meals on wheels were registered from the municipalities. Qualys were calculated as a part of the cost-utility analyses.

Mixed models were used to analyse repeated measurements, where as linear regression was used when analysing continuous data without repetition. Results are presented as mean (standard error (SE)). Discrete data was analysed with chi-square test and Newcombe`s test for differences between proportions.

Results: 397 out of 1077 patients were found eligible and included in the study, 198 in CGC and 199 in OC. 547 did not fulfill the inclusion criteria, and 54 patients refused to participate. Only 79 potential participants were not included due to other reasons.

Characteristics of the study population: 74% were women, mean age was 83 years, mean pre-fracture BI was 18 points and the mean NEAS was 41 points.

The primary outcome as mean score of SPPB at 4 months was 5.12(0.20) in CGC and 4.38(0.20) in OC. (Group difference (GD) = 0.74; CI 0.18 to 1.30; p= 0.01).

Index stay: SPPB at 5th postoperative day was 1.61 (0.19) in CGC and 1.04 (0.20) in OC. (GD= 0.56; CI 0.20 to 1.10; p=0.042).

One month: FESI was 12.73(0.35) and 13.97(0.37) in CGC and OC; (GD=-1.24; CI-2.24 to -0.24; p=0.015). Outcomes not referred at one, four and 12 months were not significantly different between the groups. Scores are referred as mean for CGC and OC respectively.

Four months: BI 16.31(0.29) and 15.30(0.29);(GD 1.01; CI 0.21 to 1.81; p=0.013), NEAS 33.59 (1.29) and 27.42(1.31); (GD 6.17; CI 2.57 to 9.78; p=0.001), FESI 11.31 and 12.57;(GD=-1.27;CI -2.27 to -0.27; p=0.013);EQ-5d 0.54(0.03) and 0.46 (0.03); (GD=0.08; CI 0.01 to 0.15; p=0.033).

12 months: SPPB 5.30(0.21) and 4.61(0.22); (GD=0.69; CI 0.10 to 1.28;p=0.023), MMSE 24.13(0.46) and 22.69(0.49); (GD=1.44; CI 0.12 to 2.77;p=0.033), BI 16.46 (0.29) and 15.33 (0.30) (GD=1.13; CI 0.31 to 1.96; p=0.007), NEAS35.20 (1.33)and 28.81(1.41); (GD=6.39; CI 2.59 to 10.19; p=0.001), FESI 10.81(0.36) and 12.03(0.39; (GD=-1.21; CI -2.21 to -0.18; p=0.021), EQ-5d 0.52(0.03) and 0.45(0.03); (GD=0.07; C! 0.02 to 0.16; p=0.015) and quality adjusted life years by QALYs 0.49 (0.02) and 0.42(0.02);(GD 0.07; CI 0.01 to 0.13; p=0.019).

LOS was 12.6 (0.43) and 11.0 (0.54); (GD= 1.6; CI0.20 to 2.93; p= 0.025); the number discharged to own home in CGC and OC was 47/198 and 20/199; p=0.001). Time in hospital after index stay 5.63(11.76) vs 8.35 (15.90) days; (GD=-2.72; CI -5.48 to 0.04;p=0.05), use of rehabilitation 21.82 (24.44) vs 25.94 (29.46) days; (GD=-4.12; CI-9.52 to 1.29; p=0.14) and in nursing homes 51.74 (104.88) vs 65.38 (114.64); (GD= -13.65; CI -35.36 to 8.06; p=0.22).The use of home- care services 103.91(168.83) vs 63.70(130.38) hours;(GD= 29.50; CI 9.72 to 69.28; p=0.0095).

The results of the cost utility analysis reported in Paper 2 found the intervention cost-effective[*].

Discussion: CGC was superior to OC being more clinically effective than standard treatment. The effects were present already during the index stay, and were maintained for one year. The differences for use of health care services were overall in favour of CGC, except more use of care services at home, although not significant. The cost utility analyses found the intervention cost-effective.

[*] Cost and the cost utility analysis published in this paper is a part of another thesis and will therefore not be discussed any further.

5.3 Paper III

Background: Observational studies in prognosis of hip-fracture patients indicate that patients with a low pre-fracture function (mobility, personal and instrumental activities of daily living (p- and i-ADL) and cognition), men, patients with extra-capsular fractures and old patients do worse. There are limited data from large randomised clinical trials (RCT´s) on the overall effect of orthogeriatric treatment, and even less on effect in sub-populations of hip fracture patients. In an RCT, we found an effect on mobility, p- and i-ADL and cognition of Comprehensive geriatric Care (CGC) as compared to standard orthopaedic care (OC).

Aim: To study if there is differences in efficacy of orthogeriatric care within- and between subgroups based on age, gender, fracture- type and pre-fracture function.

Methods: The study population is the same as in Paper 2.We investigated if pre-fracture function by NEAS (high function defined as NEAS≥45), gender, type of fracture (intra (ICF) - or extra (ECF)-capsular) and/or age (dichotomized as 70 to 79 or >80) may influence the effect of CGC on mobility by SPPB, p-ADL by BI, i-ADL by NEAS, and cognition by MMSE. Clinically important differences are defined as SPPB $\geq$ 0.5 points, BI $\geq$ 1.49 points (264), NEAS $\geq$ 2.4 points) , and MMSE $\geq$ 2 points .

Collection of data and methodology is similar to Paper 2. Analyses are performed by mixed models as a three-way interaction analyses with group allocation, time and the respective subgroups created by function, gender, type of fracture or age as factors.

Results:

Within group effects:

4 months: Patients <80years had an effect in favour of CGC on SPPB (6.4 and 5.3; p=0.017), NEAS (39.2 and 27.7), p<0.0001), BI (17.2 and 15.3; p=0.003). Patients above 80 had an effect on SPPB (4.5 and 3.9; p=0.039).

Women had an effect in favour of CGC on SPPB (5.1 and 4.1; p=0.001), NEAS (33.6 and 27.6; p=0.0001) and BI (16.5 and 15.4; p=0.005). We found no effect of CGC in men.

Patients with ICF had an effect in favour of CGC on SPPB (5.6 and 4.5; p=0.001), NEAS (35.0 and 28.1; p=0.0001), BI (17.0 and 15.5; p=0.001). We found no effect in ECF.

Patients with pre-fractureNEAS≥45 had an effect in favour of CGC on SPPB (6.6 and 5.7; p= 0.006) and NEAS (44.8 and 37.4; p<0.001). Patients with NEAS<45 had an effect of CGC on BI (14.1 and 12.6; p= 0.005).

Except for the difference observed for BI in women, these statistically significant differences are even clinically important. For cognition there were no clinically or statistically significant differences at four months

12 months: Participants<80 years had an effect of CGC on NEAS (39.0 and 31.3; p=0.003) and on MMSE (25.1 and 22.9; p=0.035). Participants ≥ 80 had an effect of CGC on SPPB (4.6 and 3.9; p=0.027), NEAS (31.8 and 26.6; p=0.003) and BI (16.2 and 15.1; p=0.011).

Women had an effect of CGC on SPPB (5.1 and 4.2; p= 0.001), NEAS (34.1 and 28.2; p=0.0003) and BI (16.6 and 15.4; p= 0.003). For men we only found effect of CGC for MMSE (24.0 and 21.4; p=0.027).

There was an effect of CGC in ICF on SPPB (5.6 and 4.4; p= 0.0003), NEAS (35.1 and 28.8; p=0.0004) and BI (17.0 and 15.3; p= 0.0004).Patients with ECF had an effect of CGC on NEAS (31.7 and 27.1; p=0.045).

Among Patients with pre-fracture NEAS≥ 45 CGC had an effect on SPPB (6.8 and 6.0; p=0.016), NEAS (47.1 and 38.4, p<0.0001), BI (18.7 and 17.7; p=0.031) and MMSE (26.3 and 24.4; p=0.015).

Effects were clinically significant for all differences in SPPB and NEAS, and most results for MMSE, while the effects on BI were below the suggested threshold of clinical importance for all subgroups.

Between group effects:

Age: There is a significant effect of CGC in favour of patients aged 70 to 79 years as compared to patients ≥80 years for NEAS at 4 months (Group difference (GD) 8.50: p=0.004). The effect disappears at 12 months.

Gender: There are no between group effects between men and women at four or 12 months.

Fracture-type: There is a significant effect in favour of ICF at four months for BI (GD= 1.51; p= 0.037) and a trend for mobility by SPPB (GD=0.93; p=0.07). These results are maintained at 12 months for both SPPB (GD=1.25; p=0.021) and BI (GD=1.49; p=0.045).

Function: There are no significant between group differences at 4 months, while there is a significant effect in favour of patients with pre-fracture NEAS≥45 at 12 months for NEAS (GD=6.83; p=0.012).

Discussion:

Our results indicate that there is a beneficial effect of CGC across the subgroups of age, gender, fracture-type and pre-fracture function. All subgroups have significant effects of one or more outcomes, and most observed effects are even clinically important.

The between group analyses show that especially patients with ECF has less benefit of CGC as compared to ICF for both mobility and p-ADL. For NEAS we registered an effect of CGC in patients 70 to 79 years at 4 months and in patients with pre-fracture NEAS≥45 at 12 months.

Interpretation: We believe that our strategy of identifying short and long time goals for patients for functional results might support recovery even if it takes time. The results for ECF might indicate that the larger trauma and following surgery is more determinative, and the benefit of CGC is insufficient to cover the difference.

To conclude, our results indicate a widespread beneficial effect of CGC, but the results seem to be better in patient subgroups with a known good prognosis while there is need of further research, especially on ECF, of males, and patients with functional decline before the fracture.

6. Discussion

The overall aim of the Trondheim Hip Fracture Trial was to investigate if comprehensive geriatric care (CGC) performed in an orthogeriatric ward was beneficial as compared to conventional orthopaedic care (OC) in an orthopaedic ward. (315)We performed a randomized parallel group clinical trial to study if a model with a geriatrician led orthogeriatric ward (Model 3 in the introduction) improved outcome as compared to a traditional orthopedic treatment for home-dwelling patients over 70 years of age who had been able to walk before the fracture. CGC had a beneficial effect on the primary outcome of mobility at 4 months, and we also found an effect on several important secondary end points as p- and i-ADL, cognition, fear of falling and quality of life at four and 12 months. LOS was increased for the index stay in CGC, but the overall time in hospital over a year was reduced for CGC. More patients were able to be discharged home, and there fewer days in nursing homes and rehabilitation institutions. However, patients treated with CGC had more use of home-based services. In post hoc analyses we explored if age, gender, fracture type and pre-fracture function was of importance for efficacy of CGC. We found that patients in all sub-groups had some effect of CGC. Patients with ICF had a significantly better effect than patients with ECF for mobility at 4 and 12 months ADL. Patients with pre-fracture-NEAS ≥45had significantly better i-ADL one year after CGC compared with patients with pre-fracture NEAS<45.

6.1 Results

In this section I will discuss the overall results in Paper II and the subgroup analysis in Paper III. I will then try to compare our results with existing knowledge and especially against the results from the Oslo Orthogeriatric Trial as these two studies were fairly similar in respect of clinical methodology, but to some degree differed in results.

6.1.1 Mobility

Mobility at 4 months by SPPB was the primary outcome of the study, and the difference of 0.74; p=0.010 was in favor of CGC. The difference is clinically meaningful and probably important to achieve independence in mobility after the fracture. The result is maintained at 12 months. The intervention is therefore effective in improving mobility in a population of home dwelling elderly hip fracture patients.

There are several elements in the intervention that was aiming at improving mobility as described under methods. We focused on early mobilization, and activity monitoring during the index stay show that patients were mobilized more frequently and for a longer period in CGC as compared to OC.(316)The orthogeriatric intervention started immediately after transfer from the emergency room, and it is possible that early intervention and increased detection of medical problems besides the hip fracture may have improved patients' general health status and well being, allowing for early mobilization. Effective pain management and focus on pain during activity was probably also important. The multidisciplinary team allowed for an early identification of patients with slow recovery after surgery, undiagnosed medical disorders and evaluation of the patients' drug regimens, and allowed for an immediate extra effort when needed. Optimal devices for supporting ambulation and function were adjusted by physical and occupational therapists. The structure of the team and the regular meetings may also reduce the risk of conflicting information from different members of staff, increasing patient confidence during single contacts with team members.

There are limited data on effect of orthogeriatric care on mobility from earlier studies. Models with geriatric consultations report improved walking ability after the treatment program, (179)and a British group reports better ambulation after implementing an orthogeriatric care pathway within an orthopedic ward.(198) An Israeli study of treatment of hip fracture patients in a geriatric ward found no significant improvement of mobility as compared with

standard orthopedic care followed by rehabilitation, but patients in the geriatric group needed less time in institution to achieve their mobility.(317)There are publications indicating detection of more complications in orthogeriatric units as compared to standard care, (217) but we have no data supporting this as an explanation of improvement of mobility in our trial. In the Oslo Orthogeriatric Trial, that also included nursing home patients, there was an overall one point difference in SPPB, and among the home-dwelling patients they report a 2-point difference of median SPPB score 4 months after surgery (p=0.04),both in favor of the intervention group,(48) . The differences reported in the Oslo trial are quite large and within the range of clinical significance despite the lack of statistical significance. Based on these two studies we conclude that mobility is improved when home-dwelling patients are treated with CGC.

6.1.2 ADL

CGC had a beneficial effect on p-ADL with BI scores of 1.01 and 1.13 points better than OC at 4 and 12 months respectively. This statistically significant difference is below both suggested thresholds for MCID of 1.45 and 1.85 as suggested by Hsieh. (264) There were several aspects of CGC that aimed to improve p-ADL. Daily training in p-ADL with focus on patient participation in daily routines by all members of staff was a defined part of the program, and more nurses per patient in CGC as compared to OC made this occasionally time consuming process possible. There was focus on discharge planning and especially aspects of p-ADL necessary to return to own home, for instance stair-walking with physiotherapist if the patient had stairs in- or outside their residence. Half of the patients have a close to normal BI score at the end of the study indicating that BI had a ceiling effect making it less suitable to identify effect of an intervention in a home-dwelling population, which may explain why the effect was relatively small on a group level.

Other studies have shown improvement or maintaining of p- ADL by orthogeriatric intervention both in consultation services and multidisciplinary orthopedic care,(95, 181, 200) but only Shyu have previously reported a positive long term-effect. (168) Our results are similar to these studies with small effects on p-ADL with uncertain clinical significance. Similar results were also reported from a Swedish postoperative intervention program. (235) The Oslo Orthogeriatric Trial reported ADL by BI, but found no difference between the intervention and control groups.(48)

The effect of CGC on i-ADL assessed by NEAS was large with a difference of 6.2 at 4 months and 6.4 at 12 months in favor of CGC. This difference was highly statistically significant (p=0.001). It was also clinically meaningful and well above the level of MCID between 2.6 and 6.1 as suggested by Wu.(270) The reasons for the improvement of i-ADL are not obvious. An improvement of general health in CGC as compared to OC may allow for more activity. Elements of p-ADL, such as stair walking are also a part of i-ADL, and will benefit from training. To our knowledge this is the first time an orthogeriatric intervention shows an effect of i-ADL. The Oslo Orthogeriatric Trial also reported on i-ADL, but their population with many nursing home patients made a measureable effect unlikely. In their home-dwelling population they report a difference in favor of the acute geriatric ward of 4.5 points, but this was not statistically significant (p=0.35).(48)

If we summarize all elements of ADL, there are some common factors. It might be a direct result of improved mobility as shown by SPPB because 3/10 items in the BI, and 6/22 items in NEAS measures aspects of mobility. Since we have an effect on mobility, this will improve ADL as well. The effect on cognition was less obvious, as discussed below, but would also improve ADL and especially i-ADL. Finally, focus on motivation and the importance of ADL to return to previous place of residence might have a positive effect.

6.1.3 Cognition

There was a small overall effect of treatment with CGC on cognition. At 12 months the patients treated with CGC had 1.4 points better average score of MMSE which is statistically significant, but below the 2-points threshold suggested as a clinical effect on an individual level.(277) Except for Alzheimer populations there are no reference data on a group level even in geriatric patients, but the difference found in our study is likely to represent a clinical effect on difference of cognition between groups. For CDR there was a difference in favor of CGC, but this was not statistically significant neither at 4 nor 12 months. CDR is not very sensitive to change, and is generally more useful to stage dementia than to follow response of treatment or progression.(318)

It is unlikely that the difference between the groups may be explained by difference in pre-fracture cognition. The pre-fracture CDR was 2.7 in both CGC and OC indicating no baseline difference. Theoretically differences in type of fracture and surgery could create a different strain on the brain in the acute phase of fracture, but there were no such differences between the groups. The CGC, however, focused on clinical aspects that can theoretically prevent and/or improve delirium.

It might therefore be hypothesized that the difference in cognition at 12 months may be explained by frequency, duration and severity of acute post-operative delirium.(63) However, we have not collected data on delirium that could help us to verify this hypothesis. Other possibilities are removal of potentially harmful drugs in CGC or improvement in general health including the trend towards less depressive symptoms that could affect the score of MMSE in CGC. A study from Boston investigated acute cognitive function after hip fracture and found less delirium after geriatric consultations (1 case of delirium avoided for every 5.6 consultations), (122) but this study did not try to show improvement of long-term effects. In the Oslo Orthogeriatric Trial the frequency of delirium was very high, more than 50% of patients in both arms had delirium during the index stay, but they also included nursing home patients who might be at a particular high risk, (54) and more than 50% of their participants had a diagnosed dementia at admission. However, they failed to show any difference in delirium or improvement of cognition during follow-up.

There are few studies reporting long-term effect on cognitive performance by orthogeriatric treatment, only Shyu found improved long-term cognition as compared to standard care. (177)The Oslo Orthogeriatric Trial had cognition after four months as their primary outcome, but failed to show any short- or long term effect on cognition. Our results are promising, but more research is needed to conclude if CGC or other orthogeriatric treatment models improve long time cognition.

6.1.4 Use of health care services

The overall difference of in-hospital time was in favor of CGC although not significant. The increased LOS was unexpected as most previous studies indicate a reduction by CGC.(96, 200, 201, 203), but also the Oslo Orthogeriatric Trial had longer mean LOS in CGC.(48) An orthogeriatric consultation study from Canada (Table 1a) also reported increased LOS, but found no difference in overall time in institutions including rehabilitation after 6 months.(175) The clinical methodology in the two Norwegian studies is fairly similar even if the populations differed, suggesting that CGC per se may be more time consuming than standard care. CGC may improve detection of complications or underlying conditions that make further treatment necessary. Less time spent in hospital after CGC may support this. It is also possible that the intention to discharge as many patients as possible back to their previous place of residence may have caused increased LOS as one extra day in hospital allowed more patients to return home without further rehabilitation. In some cases it was concluded that they were unlikely to benefit from rehabilitation. These patients had to wait in hospital for discharge to a nursing home instead of being discharged to a rehabilitation facility

at an earlier stage . In the OC occasionally lack of beds may have forced surgeons to discharge patients early despite possible benefit of longer stay in hospital.

Patients in CGC spent fewer days in rehabilitation institutions than patients from OC, but the difference was not statistically significant. It may be that patients with poor potential for rehabilitation were discharged directly to nursing homes. In addition to factors mentioned previously, this may also be related to better discharge planning, or better function reducing the need of rehabilitation in institution, and thereby an increased number of patients could be discharged directly home. There are limited reports in literature of rehabilitation after orthogeriatric treatment. Studies in stroke patients indicate a long term benefit of early supported discharge as compared to standard care, (319) but we have not identified such studies in hip-fracture patients. The results from studies of home-based physical therapy are so far inconsistent. (320) Our group is currently investigating the effect of individualized home based rehabilitation as compared to standard care in a new RCT.(321)

The use of services in the municipalities showed more days in institutions after treatment in OC, and more use of home-based services after CGC. There were significantly more patients needing a short time stay in a nursing home in the OC population after the post acute phase, probably indicating increased functional challenges as observed for mobility and NEAS. Increased use of home-based services may indicate that the CGC identified more challenges for the patients prior to discharge, or at least provided better discharge planning and it is possible that this affected future need of institutions.

6.1.5 Other

Quality of life was in favor of CGC at both 4 and 12 months. This difference was clinically and statistically significant and supports findings in previous studies of orthogeriatric treatment.(6, 322, 323) As both mobility and ADL was improved by CGC, this is likely to affect EQ-5d. We also had focus on treatment of pain, and in a paper currently under review we found more use of opiates in the CGC.(324)

The mortality at 12 months was 30 (15.2%) and 37(18.6%) in CGC and OC, respectively. This difference was not statistically significant but is similar in a previous non-randomized study of geriatric managed orthogeriatric care (Table 1c).(220) On the contrary, the Oslo Orthogeriatric Trial had a higher mortality, 46(28.2%) in the intervention as compared to 43(25.9%) in the control group. The discrepancy between our results and the Oslo study most likely reflects differences in case-mix.

There is very limited evidence from orthogeriatric trials that orthogeriatric treatment is effective in reducing depression, (178) although multidisciplinary rehabilitation as compared to standard care has been shown to improve depressive symptoms.(325) In our material there was a trend towards improved mood after CGC. A Dutch study found increased risk of depression after hip-fracture surgery in patients with delirium,(326) and as for cognition reduced frequency of delirium could result in better scores of GDS. More research is necessary to prove an effect of CGC on mood disorders after hip-fractures.

CGC significantly reduced fear of falling at both 4 and 12 months in our study. This could represent an important finding if patients changed behavior due to difference in fear of falling. Earlier studies have shown a strong correlation between FESI score and physical function in geriatric populations, (327) and it is likely that there is a similar relationship for FESI-s. On the other hand both CGC and OC had scores of FESI-s in the same level (9-13) indicating moderate risk of falling in both groups and therefore some degree of uncertainty of the clinical impact of our results.(289) FESI-s is sensitive in patients with low function, while it has a ceiling effect in high-function patients. It is possible that the effect we observe in our material reflects an effect in the frail part of our population, which our

other assessment methods may miss. We have not, however performed any sub-group analyses on FESI-s, so this question remains unanswered.

6.1.6 Subgroup analysis

There is very little, if any, evidence from previous orthogeriatric studies on which patients benefit from interventions. In Paper III potential subgroup effects of CGC have been analyzed in four subgroups (age, gender, fracture type and function by i-ADL). Old age, male gender, extra-capsular fractures and poor pre-fracture function are established risk factors for poor outcome (death or functional reduction).(309, 328) As for function previous studies have identified 3 groups with different outcome; independent patients with normal or only slightly reduced i-ADL ("well- functioning") that does well, patients with reduced i-ADL but independent in p-ADL ("intermediate function") and dependent patients with reduced p-and-ADL("low function") who do poorly. (41) Most home-dwelling patients will be in the first two groups, while most nursing-home patients will be in the latter. We postulated that CGC would mainly benefit those in the intermediate group, while well-functioning patients would recover after the hip-fracture regardless of allocation. The results from our sub-group analysis do not confirm our theory, as the well-functioning patients actually benefitted the most of our intervention.

Patients aged 70 to 79 years seem to benefit more from CGC for i- and possibly also p-ADL at four months as compared to older patients. This effect disappears at 12 months. The between group difference for i-ADL might be affected of use of institutions after the index stay as all patients would have a low i-ADL score during an institutional stay. It is possible that older patients used more institutional services, which would affect i-ADL. This should not affect p-ADL to the same degree, but even for p-ADL there is a clinically important difference in BI of almost 2 points which also disappears at 12 months. One explanation is that patients ≥ 80 needs more time to recover, while patients <80 improved earlier. The improved long term recovery in CGC might also be a result of better discharge planning including realistic treatment goals and programs to reach the goals at discharge. Improved general health might also play a part. Based on our data CGC is superior to OC irrespective of age, but the magnitude of effect is largest in the younger age group where the differences are highly significant even in a clinical setting for all outcomes.

Female patients have statistically significant benefits of CGC at 4 and 12 months. The effect on mobility and i-ADL are clinically significant, but not as impressive as for instance the effect of CGC on i-ADL for patients aged 70 to 79. Male patients, on the other hand, fail to show any benefit of CGC at 4 months, but have a clinically and statistically important effect of CGC on cognition at 12 months and a clinical effect even for i-ADL. The between-group interaction analysis did not confirm the gender difference suggested by the within group analyses, even if there is a trend in favor of women for mobility at 12 months. A possible explanation of both the within- and between group results are lack of statistical power as the minority of patients are men. The uneven size of the groups could create a type II error in respect of between group differences, while the small size increases the risk of type I errors as well for the within group differences. However, except for cognition, most results in OC and CGC are almost identical in males, making a type I error less likely. If men benefit less of CGC, there are several possible explanations for this. Some previous materials have suggested that men benefit more from active rehabilitation than females,(329) and more use of rehabilitation in OC may have closed the gap between arms seen in the overall material. Male hip fracture patients are less likely to live alone than female patients, and this may reduce the benefit of good discharge planning in respect of home care as the patient receive necessary assistance anyway. In either case this would reduce the benefit of CGC as compared to OC. Another possibility is that traditional hospital treatment actually is more suitable for men, and that the additional benefit of CGC is therefore limited. Further research is needed to improve hip-fracture treatment for men as they still have a worse prognosis compared to women.

Patients with intra capsular fractures have a clear clinical and statistical effect on mobility, p- and i-AD at both 4 and 12 months, while patients with extra-capsular fractures only have a moderate effect of i-ADL at 12 months. The interaction analysis support this with statistically significant or trends of differences between the fracture types at both 4 and 12 months for mobility and p-ADL. One possible explanation is that the impact of the extra-capsular fractures on mobility and function is so determinative that the possible beneficial effect of CGC only marginally affects prognosis. Patients with extra capsular fractures have more soft tissue injury as a result of the trauma and also due to a larger surgical trauma, and it is possible that they benefit from a less intensive mobilization regimen especially in the early postoperative phase. Previous studies have shown that patients with extra-capsular fractures have a worse prognosis than patients with intra capsular fractures,(92) but there were indications from non-randomized studies that orthogeriatric care was beneficial.(317) Our data do not support these findings, and further research is necessary to conclude with respect to CGC and extra-capsular fractures.

The results from the analysis in subgroups based on pre-fracture NEAS showed that the well-functioning patients profited most from CGC. This is consistent with the results in the other analyses that patients with the best prognosis profited most, and undermines our theory that CGC would especially improve outcome in patients with functional limitations. Those with the highest function had a considerable clinical improvement that was statistically significant in all outcomes at 12 months and most outcomes at 4 months. Patients with pre-fracture NEAS <45 only had a small clinical effect of BI at 4 months and no clinically relevant long term effects. The between-group analysis supports the results in the individual tests with a significantly better effect of CGC in the well-functioning group after 12 months for NEAS. There might be several explanations to our finding. Efforts to reduce cost and improve quality in care for the elderly have made it possible to stay at home longer, and home-dwelling patients may be more physically reduced before the fracture compared to previous studies and to some extent represent the low function population and not the intermediate. We divided our material by median pre-fracture-NEAS to get maximum power in the sub-group analysis, but patients with a lower score in the well-functioning group might actually represent the intermediate group as defined by Ranhoff.(41) A clinically founded group based on NEAS, for instance of 60 points, would have eliminated that, but instead have created power issues. A third explanation is of course that the patients with the best pre-fracture function has the greatest potential for recovery, at least with our assessment tools, and that CGC preserves their reserves in a superior way to OC. All hip-fracture patients have a limited expected life-span, but especially well functioning patients have years to live, and improvements in mobility, p- and i-ADL and even cognition could improve quality of life and reduce the needs for use of public services in the remaining time after the fracture.

6.2 Methods

In this section I will discuss aspects of validity in respect of the methods used in our study. I will also discuss clinical methods, our use of outcomes and statistical methods.

Internal validity is described as the degree of which the results are compromised by systematic errors (bias).(330) The four systematic errors that may compromise the result are errors of selection (patients with a better prognosis is selected for one arm) , performance (patients in one arm receive better care or follow-up), detection (biased assessment of outcomes) and attrition (biased occurrence and handling of protocol violations and loss of follow up).(330) Most journals uses the CONSORT criteria and checklist to ensure that internal validity is good, and that the research is transparent in respect of methodological weaknesses.(246, 331)

External validity is the degree of which the results are valid not only in the study but in different settings as well. External validity can only be evaluated if internal validity is good.(330)

6.2.1. Internal validity

This is a prospective RCT with parallel groups which is a robust and recognized scientific method. We used computer based randomization with unknown block size to eliminate the possibility of manipulation of the results. In retrospect we learned that the blocks were fixed due to an error in the Unit of Applied Clinical Research, NTNU, but as this was unknown during collection of data and inclusion of patients, we do not believe that it will compromise our results .The inclusion rate was less than expected, and only37% of patients screened actually entered the study. The numbers of errors related to the randomization procedure are small, and should be divided equally between groups (patients not randomized at all).The limited numbers of beds in CGC occasionally generated a stop in recruitment to the study and all patients were admitted to the OC ward but did not participate in the study. We therefore believe that there was no risk of selection bias in this study.

The treatment was not blinded and this is probably the largest weakness of our study. It would of course be impossible to blind participants, but we might have blinded at least the assessors.(219) Lack of blinding due to treatment could cause performance and selection bias.

Differences in facilities could represent a potential performance bias during this trial. New and patient friendly facilities in CGC during the first half of the study could stimulate patients and staff to deliver the extra effort necessary to regain function. On the other hand, the OC received new facilities in the second part of the study with possibly a similar effect. Our efforts to investigate the possible effects did not show any significant effect of new facilities, but there was a trend to better CGC performance in the first half and OC performance in the second half. The CGC team and the OC team worked separately without any collaboration, and neither group would be able to influence treatment given by the other, and we find it likely that both teams would try to deliver the best possible care available. One possible exception would be surgery, where the responsible surgeon could choose surgery dependent of allocation, but there are no indications that this has happened. Patients not randomized into the trial, were admitted to OC, and in periods of high turnover this could create some degree of performance bias due to more patients per staff, but the effect is probably small as the hip fracture patients only are a part of the total trauma population. The overall risk of a performance bias in this study should be small.

A detection bias is possible since the same group of assessors tested outcomes in both groups both at baseline and during follow-up. We have tested if there is any difference in scores from assessors who tested the participants both at index stay and during study assessments at 1, 4 and 12 months, compared to patients tested by different assessors, but found no difference. The assessors collecting data from municipalities were blinded. Regarding collection of data on use of services from national registries, there should be no risk of detection bias. Testing outside the planned test period as defined under 3.1.2.1 Study related assessments, could represent a detection bias as the patients results to some degree depend on days since surgery. A limited group of patients were tested outside the the predefined test periods due to error or other reasons. We choose to use all results at the 5^{th} postoperative day, 1 month and 4 months as the deviations were very small and there was no difference between CGC and OC in number of patients tested outside at any test point. At 12 months data of one patient in each group was discarded as they were tested considerably outside the test period, and actually died before they entered the period. As results from clinical tests, questionnaires and the data from the municipalities show similar results, we find it likely that any detection bias at least is small.

In most studies including ours there are deviations from protocol that could represent attrition bias. In the protocol paper, the number of included patients is 401, (219)and Paper I describes 398 included patients.(249) At the time of publication of the protocol, we had not started to look into any data, and the number of 401 was registered in the randomization engine. However, later inspection of the data revealed that 3 patients were randomized twice by error

in the emergency room leaving 398. One patient was later removed from the data analysis as she already had a permanent residency in a nursing home by the time of admission leaving 397 participants. Her data was removed before any analysis of outcomes was performed including her allocation and should not represent an attrition bias. There were more withdrawals in OC as compared to CGC (6 and 13 at 12 months). We consider these numbers to be small. Loss to follow-up at any time point was fairly similar between groups. If withdrawal or loss to follow-up was MNAR, for instance patients with poor health due to treatment were more likely to withdraw than those in good health; any effect would be in favor of OC and reducing the measured effect of CGC. We therefore conclude that it is unlikely that the observed difference in favor of CGC is flawed by attrition bias.

Our overall evaluation of internal validity is that there are no obvious biases in selection, and that any bias in performance detection and attrition are most likely to be small even if we have not completely ruled out possibilities for these.

6.2.2 External validity

External validity may be described as "To whom does the results of this trial apply?"(332) Several aspects affect external validity and the generalizability of the result from an RCT:

- The setting of a trial.
- The selection of patients
- Characteristics of randomized patients.
- Differences between trial protocol and routine practice
- Outcome measures and follow-up
- Adverse effects

6.2.2.1 Setting

This was a single-site trial in a large university hospital. The practice in the hospital is fairly similar to other Norwegian hospitals. It is a public hospital, and due to training a large part of surgery is performed by junior surgeons. This setting is fairly typical for hip-fracture surgery in Scandinavia and probably even Western Europe.

Our study population is a mix of rural and urban participants, but with most patients from the City of Trondheim which is a large city in Norway (169 000 inhabitants in the city, 182 000 in the entire municipality). Most of the other patients are from mainly agricultural municipalities. Patients from small towns are represented to a limited degree. Our population is representative for a Norwegian hip fracture population. Most other orthogeriatric trials recruit their populations from large cities surrounding the hospital. (48, 96, 190) Therefore, participants from rural areas increase the external validity of the study.

6.2.2.2 Selection and characteristics of patients

Patient selection and characteristics are important for external validity. An unselected population with no or few exclusion criteria has a high external validity, but the risk of not identifying effects due to confounders or feasibility issues increases. We wanted to study effect of mobility and place of residence, and our patients had to have pre-fracture ability to walk and could not have a permanent institutional position due to this. We choose 70 years as our lower age limit. We believed that younger patients to some degree would object to treatment in a geriatric ward, even if there is some evidence that younger hip fracture patients share many characteristics with older patients, and also have an excess mortality and morbidity as compared with age matched patients without fracture.(2) We wanted to study short and long time effects, and the primary end point at 4 months was chosen as a compromise between clinical stability (some patients are still improving) and power (more patients alive than after a year). As a

consequence of this we also excluded patients with an expected survival of less than 3 months. High-energy trauma patients were excluded as they are a different entity as compared to fragility fractures.

A total of 680 patients were excluded from the study, 250 due to nursing home status and 154 were younger than 70 years and only 143 due to other exclusion criteria. Only 54 refused to participate. As many as 79 patients did not participate without known reason. As they do not contribute to any arm in the RCT, this should not represent a selection bias, but could possibly affect the composition of our population and affect external validity, for instance if they shared any characteristics as gender or function. As we have no data on these patients, we can not exclude this possibility. Most of these patients were not randomized due to lack of available space in CGC, and this would make lack of inclusion a random event that would not affect validity. If patients were not included due to an active choice in the ER, for instance due to opinions that functionally fit patients do not belong in CGC, the threat to external validity would be of more concern, but we have no obvious indications that this was the case. Our vigorous follow-up of admissions and late randomizations of patients passing ER without randomization should also make this problem limited. The average age of patients in our study was 83 years. This is similar to most recent hip fracture studies, even if our limit of 70 years of age is higher than most studies. Most orthogeriatric trials have participants with a mean age in the early eighties. One exception is the Taiwanese trials where patients were in their seventies, (333) while populations that include nursing home patients are somewhat older.(48)

Previous publications suggest that one third or more of hip fracture patients are permanently institutionalized.(48, 211) Exclusion of nursing home patients affects external validity of the study, but we still think it was necessary and have made it possible to identify important effects in the home-dwelling population. However, only 23% of patients screened in our material were actually residents in nursing homes. This may suggest a healthier than normal population in our catchment area or more likely, a higher threshold to be admitted into a nursing home for instance due to improvement of home-based care in recent years or lack of available rooms in institutions. This would increase the external validity of the study, and may explain why our “low-function” group benefitted less than anticipated of CGC. The Oslo Orthogeriatric Trial did include nursing home patients, but failed to show an effect of their primary outcome at least in part due to the case-mix of their population.(48)

6.2.2.3 Differences between protocol and routine practice

In this study, differences in treatment (“performance”) and its effect of outcomes are the subject actually studied. The clinical treatment during CGC is described under the methods section. I will discuss a limited numbers of elements in the clinical treatment.

Comprehensive Geriatric Assessment (CGA) is widely used and found effective in a meta-analysis investigating geriatric care.(165) The data on CGA in orthogeriatric treatment is more limited, but in a fairly recent meta-analysis the conclusion is that a multidisciplinary intervention is likely to be beneficial.(334) We have used the acronym CGC instead CGA to emphasize our focus on both assessment and treatment. The content in our model as described earlier is still similar to orthogeriatric guidelines for multidisciplinary treatment.(103) Geriatric patients often present symptoms and not a disease. Fracture patients, however, are an exception as the diagnosis is clear-cut. We had to compromise between comprehensive assessment and efficacy in our unit. Symptoms possibly relating to serious underlying disease as cancer were investigated, while less alarming findings were referred to the patient’s primary physician at discharge. There is very little information in literature on how this is practiced in other orthogeriatric units or programs.

The plan for further treatment was mainly based on pre-fracture functional status, and the adjusted according to progress, complications or other elements through daily meetings. One important element for success (return to own home functionally independent directly from hospital) was not to suggest need of institutionalization before decided

within the team. In our experience it was almost impossible to suggest differently once any member have made this suggestion. Another effect of these interdisciplinary meetings was to schedule when different specialists were to see the patient to improve work planning and reduce patient strain.

We followed a liberal transfusion strategy to prevent delirium with blood transfusion if hemoglobin values dropped below 10 g/dL as recommended by Scandinavian studies.(335) A large American study found no effect on ability to walk or mortality after 60 days by a liberal transfusion strategy, (153) but even if patients had a higher HgB in the liberal group at time of transfusion only 40% of patients in both groups got transfused. The question of liberal versus conservative strategy of anemia in hip fracture patients is unanswered, and it is still possible to defend the strategy we choose in this study.

A systematic treatment of osteoporosis was intended in our method, but many patients were referred to the hospital out-patient clinic for investigation and start of treatment after discharge .Despite this element of uncertainty, evaluation of drug use at discharge indicate that more patients received treatment for osteoporosis after CGC.(324) We intended for a vigorous follow-up on nutrition with measurement of Body Mass Index (BMI) and caloric intake assessment during the index stay in line with other orthogeriatric interventions.(232) We have not published any data on this, and unfortunately it is likely that this part of our treatment program was not as good as intended. A nutritionist was not part of the staff in the CGC ward. We did not include a systematic follow-up after discharge, which is recommended by some authors.(323)

To conclude, we believe that the content of our intervention is up to date, even if there is room for improvement. All elements of this intervention can be implemented with limited extra resources in a western society. It is likely that our results reflect a beneficial effect of CGC per se.

6.2.2.4 Outcomes and follow-up

Outcomes in a clinical trial should be relevant for the disease studied, and they should possibly be affected by the intervention given, and the tools used to investigate the outcome should be feasible and validated in the population studied.(290)

In our original protocol, we used TUG at four months as our primary end point, while this was changed to SPPB at 4 months in the final version. We discovered that TUG had a clear floor effect in our run-in period before study start, as many patients were unable to perform the test, and changed the protocol as SPPB was possible to score in all patients. SPPB may also be more sensitive to change as compared to gait speed alone, (257, 336) but we have not identified any study comparing TUG and SPPB. SPPB is a performance based tool, and possibly more reliable than a questionnaire based tool in an elderly population where many may suffer from cognitive decline.(337) Some authors argue that performance based tools and questionnaires investigate different properties, and that both are appropriate, but in different settings.(338) Performance based tools are probably better when examining changes in physical function. (338) It may be argued that SPPB is a surrogate end point as it delivers a “score” as compared to gait speed, ability to ambulate independently or having the ability to walk. While for instance gait speed can only be assessed in patients able to perform the test, the SPPB, which also includes gait speed, gives a score to all patients, even those unable to walk, thus making it possible to include all patients in the analysis. SPPB also includes activities of relevance for daily life: walking 4 meters, ability to rise from chair and standing balance, and is suitable for use in different settings and for patients at different functional levels.

We have a wide range of secondary outcomes. All instruments are presented in the Methods section, and I will only discuss a few aspects of some of the instruments below.

P- and i-ADL are measured to investigate disability and not only functional limitations.(337)NEAS is found to be reasonably reliable and feasible in elderly patients.(267, 270, 339) It is validated for hip replacement patients, but not for fracture patients. We believe that the similarity between fracture and replacement patients is acceptable for using NEAS as a measure of i-ADL. The problem with a ceiling effect described in replacement patients,(267) was not present in our material as very few patients reached maximum score .

CDR was used to measure pre-fracture cognition and also repeated two more times during the trial. It is recommended by the inventors of CDR that all assessors take an online training and certification in testing before using the test in clinical and research practice to ensure a consistent scoring between individual assessors. We have used a Norwegian translation of CDR by Engedal, where this recommendation was omitted. Even if all assessors received instructions how to score CDR, none received systematic training as recommended. This is a methodological weakness, but any deviations from ideal scoring should be equally divided between groups and should not affect the overall result.

We did use the generic EQ-3d measurement for quality of life and not a disease specific scale like Harris Hip scale. (340) Generic instruments are less sensitive to small but important changes in quality of life, but this was done to be able to perform cost utility analyses in a later stage.(290) It can be argued that we could have performed a disease specific measure as well, but we chose not to limit patient attrition.(302)

A complete registry of use of services would include in-formal resources as help of next of kin and private delivery of services.(341) In our population we believed that attempts to register such data would be difficult in this old population with increased risk of cognitive decline, and result in missing data and possibly patient attrition. The registration of use of resources and services are therefore from a health care perspective only.

6.2.2.5 Evaluation of external validity

We find our results valid for a home-dwelling population 70 years or older. These results are produced in a public Western European setting, and we can not conclude whether similar results would be produced for instance in USA. We believe however, that the methodology used in the trial is relevant and may also be used in such a setting. The main weakness is the absence of nursing-home patients, and further trials are needed in such populations to prove efficacy of CGC even in older and frailer populations.

6.2.3 Statistics

Validity can be compromised by statistical methods.(342) We have done our best to comply to standards and deliver quality also in this area.(343) This is described in the Papers II and III, and also comprehensively in our Statistics Analysis plan. We have tried to use state-of-the-art methods regarding limitations of the chosen methods, and all analyses are performed under the guidance of experienced statisticians.

Mixed models is valid even when there is missing data.(303) It is not reliable if missing data is mainly NMAR. It is likely that our missing data is affected by age, comorbidity and functions making missing data MAR and not CMAR, but we have no reason to suspect any unknown confounder that would affect the groups and creating any bias.

There is a controversy in regard of testing for imbalance in the material by performing significance testing on background variables and covariates, and we have chosen not to do so as any difference should be due to randomization.(344) Covariates were chosen due to their clinical relevance to reduce the error margin as suggested by Senn.(344)

All data in our study is collected after the fracture occurred except for CDR, BI and NEAS which collects baseline data retrospectively. We have used a mixed model including a possible effect of the intervention also at the time of the first measurement. Hence, the fact that the first data collection was after initiation of the intervention does not introduce bias in the estimates.

6.3 Areas for further research

Our model is now the best documented treatment option for this patient group, and new models and also existing models should if possible be tested in RCTs against our or a similar model. Other existing models as so-called co-managed care or clinical pathways are probably easily adapted as treatment still takes place within an orthopedic ward, and there will be no relocation of resources from an orthopedic unit to a "competing" geriatric unit, but in my opinion lack documentation.

Even if our results are promising, patients in both arms suffered from a decline in function as compared to pre-fracture status. Future studies should aim to reduce this loss further. There are good reasons to believe that more physical training between discharge and during the first year after the fracture could improve physical function. Future research should identify better rehabilitation methods, for instance methods of home based training that would give additional benefits. Our group is currently investigating this in a large RCT.(321)

Our data indicate that patients with the best prognosis still benefitted most from CGC, even if some effect was observed in all sub-groups. The analyses in Paper III are post hoc, and the results should be tested in future studies. Improving treatment even for nursing home patients and frail home-dwelling patients should also be an area of future research, and it is likely that other outcomes as control of pain or fear of falling might be more important in these populations.

6.4 Summary of discussion and conclusion of thesis

We have developed an acute orthogeriatric intervention which is clinically effective and available with a reasonable degree of use of resources and cost-effectiveness. Description of our method and results are published in peer-reviewed journals and analyzed with modern statistical methods of high standard.

The Trondheim Hip Fracture Trial has shown a statistical significant and clinically meaningful effect of CGC on the main outcome of mobility at 4 months. The effect was maintained after a year. A similar effect was found for p- and i-ADL, fear of falling and quality of life. For cognition we found a statistically significant and probably also clinical meaningful effect after 12 months.

Subgroup analyses indicate that the results were better in the patients with the best prospects at admission, and not to the same degree in patient with a poorer prognosis that we would hypothesize to benefit more from the intervention. Even if some patients may benefit less than others, the methodology presented in this thesis represent the State of the Art of hip fracture treatment of today.

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Paper I

Saltvedt et al. BMC Research Notes 2012, 5:355
http://www.biomedcentral.com/1756-0500/5/355

BMC Research Notes

PROJECT NOTE Open Access

Development and delivery of patient treatment in the Trondheim Hip Fracture Trial. A new geriatric in-hospital pathway for elderly patients with hip fracture

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Abstract

Background: Hip fractures are common among frail elderly persons and often have serious consequences on function, mobility and mortality. Traditional treatment of these patients is performed in orthopedic departments without additional geriatric assessment. However, studies have shown that interdisciplinary geriatric treatment may be beneficial compared to traditional treatment. The aim of the present study is to investigate whether treatment of these patients in a Department of Geriatrics (DG) during the entire hospital stay gives additional benefits as compared to conventional treatment in a Department of Orthopaedic Surgery (DOS).

Findings: A new clinical pathway for in-hospital treatment of hip fracture patients was developed. In this pathway patients were treated pre-and postoperatively in DG. Comprehensive geriatric assessment was performed as an interdisciplinary, multidimensional, systematic assessment of all patients focusing on each patient's capabilities and limitations as recommended in guidelines and systematic reviews. Identification and treatment of co-morbidities, pain relief, hydration, oxygenation, nutrition, elimination, prevention and management of delirium, assessment of falls and osteoporosis were emphasized. Discharge planning started as early as possible. Initiation of rehabilitation with focus on early mobilisation and development of individual plans was initiated in hospital and continued after discharge from hospital. Fracture specific treatment was based upon standard treatment for the hospital, expert opinions and a review of the literature.

Conclusion: A new treatment program for old hip fracture patients was developed, introduced and run in the DG, the potential benefits of which being compared with traditional care of hip fracture patients in the DOS in a randomised clinical trial.

Keywords: Hip fractures, Geriatric assessment, Oldest old, Randomized controlled trial, Interdisciplinary health team

Findings

Background

Hip fractures are common in elderly people [1]. Patients with hip fractures are heterogeneous with respect to age, pre-fracture function and morbidity [2,3]. Many are frail, have chronic comorbid disorders, cognitive impairment, low body weight and are functionally impaired before the fracture [3]. On admission to hospital they frequently suffer from concurrent minor or major medical conditions that may impact on prognosis [4,5].

After hip fractures a high proportion of the patients experiences reduced performance of basic and instrumental activities of daily living, reduced mobility with need of walking aids, decreased ability to move outside their own home, and they often report deterioration of health status [6-8]. A considerable proportion needs

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nursing home placement [7,8] and one-year mortality is high [1].

The Research Group on Geriatrics, St Olav Hospital, University Hospital of Trondheim, Norway, has previously performed a randomised clinical trial showing that by treating acutely sick, frail elderly patients in a geriatric evaluation and management unit, mortality was significantly reduced and the chance of living at home was improved [9-11]. Over years the group has also been focusing on research on assessment and treatment of older persons at risk of falling [12].

In 2007 the research group decided to perform a prospective randomised trial on treatment of hip fracture patients in order to investigate if treatment in the Department of Geriatrics (DG) can improve outcomes as compared to standard treatment in the Department of Orthopaedic Surgery (DOS). Primary outcome is mobility measured by the Short Physical Performance Battery (SPPB) [13] 4 months after surgery. Secondary outcomes measured at 1, 4 and 12 months postoperatively are place of residence, activities of daily living, balance and gait, falls and fear of falling, quality of life and depressive symptoms, as well as use of health care resources and survival. The complete study protocol has been described previously [14].

During the last years several studies have been performed on treatment of hip-fracture patients by geriatric interdisciplinary teams. The study design including intervention and outcomes have varied and the studies have been performed within different health care systems. To be able to compare studies and evaluate factors of importance for success it is important to describe the interventions in detail. The aim of the present paper is to report the basis for the treatment model in the Trondheim Hip Fracture Trial and to describe treatment options offered to the patients in the DG (experimental group) and the DOS (control group), respectively.

Basis for the experimental treatment

Model

During the last years new models in treatment of elderly hip fracture patients including interdisciplinary care and some kind of geriatric intervention have been introduced. The results have been summarized as systematic reviews, guidelines and meta-analyses [15-21].

The models studied have been treatment in orthopaedic wards with geriatric consultant services on request, orthopaedic wards with daily consultative services by geriatricians, initial treatment in an orthopaedic ward with transfer to geriatric wards postoperatively, and treatment in orthopaedic wards where orthopaedic surgeons and geriatricians treat patients together [17,20]. The literature is still inconclusive as to which of these models are most beneficial. However, models with an integrated approach with early involvement of a geriatric interdisciplinary team seem to be superior as compared to models using consultative services or where there is a late involvement of the geriatric interdisciplinary team [17,20].

In the present study the choice of model was based on a review of the literature and also partly being a consequence of a reorganisation in our hospital in 2007. The number of beds was cut down in the DOS reducing the total capacity of the department, therefore temporary solutions were sought to be able to care for the high number of patients admitted with fractures. Therefore, an orthogeriatric bed-unit was established in an acute geriatric ward giving us the opportunity to investigate the potential benefits of performing comprehensive geriatric assessment (CGA) on hip fracture patients in a department previously having shown its efficacy on treating frail geriatric patients in general [9]. The innovative element in this model is a DG being responsible for the medical treatment from admission to discharge, including CGA and initiation of rehabilitation, although most of the rehabilitation program was completed after discharge either at home or in a suitable institution.

To our knowledge this is the first randomised clinical trial of a model treating hip fracture patients pre- and postoperatively performing CGA in a DG with main focus on the intervention during the acute phase.

Comprehensive geriatric assessment (CGA)

CGA applied on acutely sick, elderly patients treated in specialised geriatric units has been shown to increase the chance of living at home, reduce functional decline and also the risk of nursing home placement [9,10,22,23].

Based upon the evidence from systematic reviews and meta-analyses [22-25] CGA should be performed by an interdisciplinary team of professionals specialised in treatment of elderly patients. Usually the team is comprised of a geriatrician collaborating with nursing staff trained in geriatrics, physiotherapists, and occupational therapists, and in many cases a nutritionist and a social worker. The interdisciplinary team should collaborate both informally and in regular interdisciplinary meetings to discuss the patients, developing individual care plans and defining short- and long term goals for each patient [25].

The assessment should be systematic and multidimensional to identify all relevant problems and initiate adequate assessments. Protocols and assessment tools for common conditions are recommended. Use of care plans is beneficial in order to comply with assessment and treatment. Communication with patients and caregivers throughout the hospital stay is important.

Treatment should be performed in a dedicated unit with sufficient space for patients to move around, offering available aids for mobility and self care, and calendars and clocks as cues for orientation. Discharge planning should start as early as possible. Collaboration across sectors as well as with the patient and her caregivers is necessary to achieve continued rehabilitation and a successful discharge.

In general, CGA should therefore be an optimal tool when treating frail elderly hip fracture patients.

Developing a treatment program for hip fracture patients in a new clinical pathway

While the DG had extensive experience in performing CGA on acutely admitted geriatric patients, it was not so for the treatment of hip fracture patients within the same context. We therefore had to develop a new program taking into consideration standard routines already established at the hospital on perioperative treatment including anaesthesiological and surgical techniques, and time to surgery. Based on a literature review [16,17,26], the present guidelines of the DOS and a visit to Diakonhjemmet Hospital in Oslo [3] a new program on optimal pre-and postoperative treatment was developed.

We focused at identification and treatment of comorbidities, pain relief, hydration, oxygenation, nutrition, elimination, prevention and management of delirium, assessment of falls and osteoporosis. Programs for prevention of acute delirium, new fractures, constipation, decubital ulcers, and falls were developed [3,27,28]. A program for early mobilisation and rehabilitation was developed aiming at individualised in-hospital rehabilitation [29,30].

Clinical pathways

Patient flow

After an orthopaedic resident had diagnosed a hip fracture in the Emergency Room, patients were screened for eligibility in the study. Randomization was performed after the patients had given their informed consent [14]. For patient flow, see Figure 1.

Patients randomized to experimental treatment were transferred to the DG located in the Clinics of Internal Medicine. In Norway geriatric medicine is a branch speciality within internal medicine, and geriatricians and internists were responsible for the treatment in DG. Patients randomized to the control group were transferred to the Trauma Unit located in the DOS, and orthopaedic surgeons were responsible for the treatment.

In both groups patients were transferred to the Operation Theatre for surgery and postoperatively to a recovery unit for observation during the first hours after surgery. Afterwards patients were transferred back to the DOS or DG according to the randomisation.

Patients were discharged from the hospital as soon as they were medically stable after surgery and a suitable place of discharge was available. The DG and DOS dealt with the same municipalities and had the same options for care, treatment and rehabilitation after the hospital stay. After discharge general practitioners and/or doctors at nursing and rehabilitation facilities were responsible for treatment.

Follow-up consultations in the orthopaedic outpatient clinic were decided by the orthopaedic surgeons during the hospital stay and performed in selected patients. There was no follow-up program at the geriatric outpatient clinic. If study patients were referred by general practitioners for assessment in the geriatric outpatient clinic, this was performed "as usual" in both groups. Study-related follow-ups at 1, 4 and 12 months were performed by separate study investigators. A few patients meeting for study related assessments were in need of immediate medical evaluation. These consultations were performed by consultants in the DG.

The major part of the health care system in Norway is organised and financed by the public sector. The government owns and run the hospitals through regional health authorities. General practitioners, physiotherapists and rehabilitation institutions get reimbursement from the government and the regional health authorities. In-hospital treatment and assistance from home care nurses is free of charge. Patients have to cover costs for drugs, physiotherapy and medical treatment up to a total limit of about 200 Euros, above which all is free. Practical help in the patients' homes are charged according to income. Due to relative low costs for out-patient medical treatment and care the patients' individual financial situation is normally not determinative for choice of treatment after hospital stay.

Organization of wards and staffing

The DG consisted of a 10 bed-ward of acute geriatrics services linked to an out-patient facility. During the trial an orthogeriatric 5 bed-unit was established as an additional, but still integrated part of the acute geriatric ward. The DG was located in a new-built part of the hospital. All patients had single-bed rooms. There were no corridor-beds. The department had a separate dining room and the corridors were suitable for moving around. As far as possible an "enriched" environment was created to enlighten the patients' orientation [28]. This included use of visible calendars and clocks in all rooms, naming plates and signs on the doors, sufficient lightening, and access to necessary aids (including hearing aids) and to news (television, newspapers, and magazines).

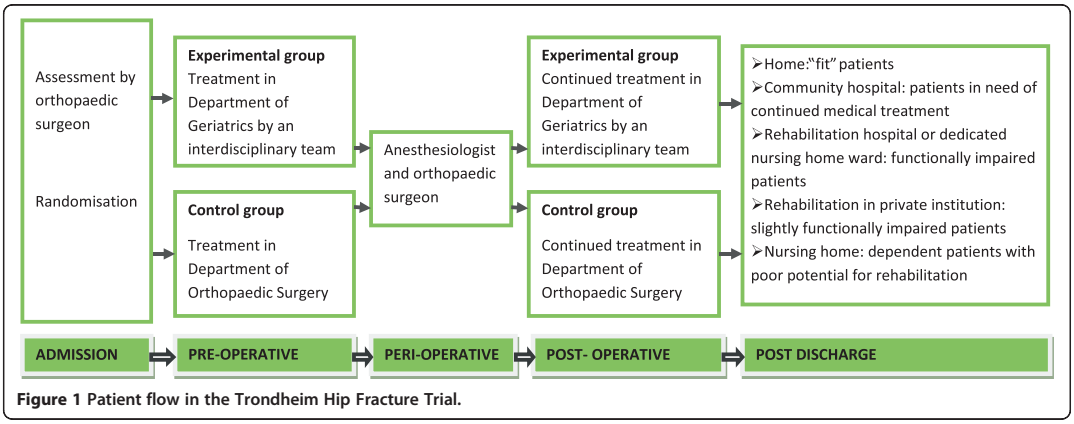

Figure 1 Patient flow in the Trondheim Hip Fracture Trial.

In the DOS patients were bedded in the Trauma Unit. During the first part of the study the DOS was located in an old part of the hospital with 19 beds in single-, double- and four-bed rooms with commonly use of additional corridor-beds. The DOS moved into a new hospital building in September 2009 having similar facilities as the DG. At the time of this transfer 219 of 398 study patients had been recruited.

The staff in both departments consisted of doctors, nurses, assistant nurses and physiotherapists. The DG also had occupational therapists. The number of positions per bed for the different professions is shown in Table 1 demonstrating that the DG was generally better staffed than the DOS.

The head of the DOS was involved in planning of the study. Both orthopaedic surgeons and other personnel categories of the DOS participated in training of doctors, nursing staff and physiotherapists in the DG both during the four month run-in period and also the initial part of the study. The educational program involved lectures and bed side practical training. Later the staff in the DG had regular teaching on issues relevant for treatment of elderly hip-fracture patients.

Orthopaedic surgeons assessed patients in DG on request; vice versa geriatricians assessed patients in the DOS on request.

Standard treatment

In the Emergency Room all patients underwent a standard general clinical examination by an orthopaedic resident, with additional blood samples, measurement of blood pressure, temperature, pulse, oxygenation and an electrocardiogram. Femoral neck fractures were classified according to the Garden classification system [31]. The resident notified the anaesthesiologists and the Operation Theatre.

Table 1 Organization of treatment in Department of Geriatrics (DG) as compared with the Department of Orthopaedic Surgery (DOS)

	Experimental group	Control group
Department	Clinic of Internal Medicine,	Clinic of Orthopaedics and Rheumatology
	Department of Geriatrics (DG)	Department of Orthopaedic Surgery (DOS)
Facilities*	Single bed rooms	Before relocation: single, double or four –bed rooms
		After relocation: single bed rooms
Number of beds in the ward	15	19 before / 24 after relocation
Organization of ward	5 beds dedicated for hip fracture patients allocated to one single cluster	Hip fracture patients spread among other patients
Staff working bed-side (number per bed)	Nurses/assistant nurses: 1.67	Nurses/assistant nurses: 1.48
	Doctors : 0.13	Doctors: 0.11 (0.08 after relocation)
	Physiotherapists: 0.13	Physiotherapists: 0.09 (0.07 after relocation)
	Occupational therapists: 0.13	Occupational therapists: 0

Patients were recruited from April 18th 2008 to December 30th 2010.
*DG was located in a new hospital building during the entire study period while DOS was relocated from an old to a new hospital building in September 2009 (as 219 of 398 patients were recruited).

All patients received intravenous saline or Ringer's acetate at admission. Low molecular heparin (enoksaparin) was given as thromboembolic prophylaxis from admission to hospital to 14 days after surgery, 20 mg twice daily preoperatively and 40 mg once daily postoperatively . Elastic stockings were used postoperatively if patients had peripheral oedema.

All patients had urinary catheters preoperatively, being removed within 24 hours postoperatively. Pressure relieving mattresses were standard equipment in the new part of the hospital and the nursing staff focused on prevention of decubitus in both groups.

For pre-operative analgesia most patients received femoral nerve blockade. In addition, patients were routinely given paracetamol 1 g every 6 hours during the entire hospital stay, while opioids were given on demand preoperatively and regularly postoperatively.

Preoperatively all patients were assessed by an anaesthesiologist using the American Society of Anaesthesiologists (ASA) score [32]. Minor or moderate medical disturbances did normally not cause delay of surgery, while in cases with medical disorders such as unstable cardiac problems, a severe infection or pulmonary embolism surgery was delayed until stabilisation was achieved. The operability was decided by the anaesthesiologist in collaboration with the orthopaedic surgeon, and in the experimental group also with the geriatrician. Sometimes other specialists were involved such as cardiologists if unstable cardiac disorders or murmurs were found. To avoid complications during anesthesiological and surgical procedures patients using therapeutic doses of heparin, clopidogrel or warfarin were postponed until the risk of bleeding was normalised. Patients using clopidogrel had to wait five days before spinal anaesthesia was considered safe, while patients on warfarin got vitamin K and were ready for surgery when INR was 1.8 or less [33]. Logistic problems within the hospital were the most common cause of delay.

Most patients received spinal anesthesia. For Garden type 1 or 2 fractures most patients were treated with a two-screw fixation but in some few cases hemiprosthesis were used. Garden type 3 or 4 fractures were treated with hemiprosthesis. Pertrochanteric fractures were treated with a sliding hip screw system (Dynamic Hip Compression Screw, DHS, or Compression Hip Screw, CHS). Subtrochanteric fractures were treated either with DHS/CHS (most cases) or antegrade intramedullary nailing. Most patients irrespective of fracture type were allowed full weight bearing postoperatively. Prophylactic antibiotics (cephalotin) were given to all patients, except those getting a two-screw fixation.

Postoperatively the patients were observed in a recovery ward until they were able of moving both legs and their medical condition were stabilised, normally about six hours after surgery.

Table 2 Comprehensive geriatric assessment at the Department of Geriatrics

Dimensions assessed	*Somatic health* – concurrent injuries or medical conditions, drug regimen, pain, falls, osteoporosis
	Mental health - cognition, depression, anxiety
	Function - ADL, IADL, mobility, sensory loss, elimination
	Social situation - place of residence, network, caregiver burden
Interdisciplinary team work	Dedicated responsibilities
Interdisciplinary team meetings	1st day postoperatively: plan for individual treatment, goal setting, discharge planning,
	4th day postoperatively: evaluation, discharge planning
Systematic approach	*Checklists*
	Treatment protocols
	Assessment scales (Barthel Index, Cumulated Ambulation
	Score: Confusion Assessment Method, Verbal Rating Scale)
Mobilization/Rehabilitation	Mobilization out of bed 1st day postoperatively
	Individualised plan for mobilization and participation in ADL being integrated in care plans and ward activities
Discharge planning	Collaboration with patient, caregivers and municipality
	Mapping of pre-fracture function, place of residence and social situation
	Discuss discharge destination 1st day postoperatively
	Set realistic short- and long-term goals
	Organize institutional care, aids, assistance, physiotherapy when appropriate

ADL – Activities of Daily Living. IADL- Instrumental Activities of Daily Living.

Treatment in the experimental group

Comprehensive Geriatric Assessment (CGA)

CGA was essential in treatment of all patients in the DG (Table 2, Table 3). The aim was to offer as good treatment as possible within available resources, to prevent complications, start rehabilitation as early as possible, and plan for discharge from hospital and further rehabilitation. The work-up focused on assessment and improvement of the patients' somatic and mental health, functional status and socio-/environmental situation.

The patients' status before the hip-fracture was mapped by the nurses and the occupational therapists by interview with the patients, and with permission from the patients, also with the care-givers and the Home Services. Information on pre-fracture cognition, activities of daily living (ADL), and instrumental ADL (IADL), mobility, nutrition, living situation, caregiver distress, participation in social activities and assistance needed from the Home services was retrieved. This information was important to make an individual plan for each patient.

Table 3 Medical treatment in the two groups

	DOS	*DG*
Hydration		
Intravenous fluid preoperatively	*V*	*V*
Monitoring fluid intake postoperatively		*V*
Perioperative antibiotic prophylaxis	*V*	*V*
Thromboembolic prophylaxis	*V*	*V*
Nutrition		
Assessment of nutritional status*		*V*
Nutritional drinks		*V*
Decubitus prophylaxis by pressure relieving mattresses	*V*	*V*
Oxygenation		
Transfusion if Hb < 10		*V*
Oxygen if saturation < 95%		*V*
Avoiding hypotension (including orthostatic hypotension)		*V*
Analgesia		
Femoral nerve block	*V*	*V*
Paracetamol 1 g every 6 h, opioids on demand	*V*	*V*
Pain assessment during rest and activity by VRS		*V*
Urine		
Removal of catheter within 24 h postoperatively	*V*	*V*
Screening for infection pre- and postoperatively		*V*
Screening for urinary retention		*V*
Constipation		
Prophylaxis and monitoring (in cognitively impaired patients)		*V*
Delirium		
Regular assessment		*V*
Focus on prevention		*V*
Osteoporosis assessment		*V*
Falls assessment		*V*

DOS – Department of Orthopaedic Surgery. DG- Department of Geriatrics
VRS- Verbal Rating Scale.
*Nutritional status – history of recent weight loss, low body mass index, low caloric intake.

The team members in the DG had separate responsibilities. A close formal and informal collaboration between team members was emphasised. Brief interdisciplinary team meetings were held the first postoperative day to discuss the process of early rehabilitation, need of further investigations during the hospital stay, and to set realistic short- and long-term goals and plan for discharge. After three working days a brief follow-up meeting evaluated if progress was as expected aiming at decisions on site of destination and day of discharge.

The in-hospital rehabilitation focused on early mobilization and weight bearing exercise programs, if no restrictions had been made from the orthopaedic surgeon. In addition participation in ADL was emphasized. An individual rehabilitation plan with short term goals was based upon previous function, cognition, type of surgery and motivation. This was integrated with care plans and executed by physiotherapists and nursing staff. Progression was evaluated by the physiotherapists regularly and performance of ADL was evaluated by the occupational therapists on 3rd postoperative day. The long-term goal was to achieve pre-fracture function.

A systematic approach was achieved using check-lists both for each professional category and for the interdisciplinary team work and applying treatment protocols developed for the most common conditions. The following standardised assessment tools were used: Cumulated Ambulation Score (CAS) [34] during the first three days postoperatively. Barthel Index (BI) [35] was scored pre-fracture, and 1st and 3rd postoperative day and at discharge. Verbal Rating Scale (VRS) for assessment of pain [36], Confusion Assessment Method (CAM) was used as screening for delirium [37], Geriatric Depression Scale was used for assessment of depression [38].

Length of stay, discharge destination and necessary arrangements for discharge were discussed within the team and with the patients and their caregivers at several occasions during the stay. Destination for discharge was based upon the patients' functional and medical status, place of living, and the patients' and caregivers' motivation. For patients living in the city of Trondheim (n = 315) a resolution on necessary actions after discharge was made in a discharge planning meeting. Both the patient, his caregivers, representatives for the municipality and nurse and doctor from the DG participated in these meetings. For the other municipalities arrangements were discussed and agreed upon through phone calls with primary health care representatives.

If possible the patients were discharged to their own home with assistance from the Home Services. For these patients physiotherapy was offered to take place either at home, in a physiotherapy clinic or at a day-time rehabilitation centre. Many patients needed institutional rehabilitation and were discharged to private or public inpatient facilities such as rehabilitation wards in hospitals or nursing homes. Some needed continued medical treatment in a community hospital, while some were too sick to be rehabilitated and were discharged to ordinary nursing home wards.

Communication with general practitioners, rehabilitation facilities and nursing homes about individual patients was based mainly upon written discharge reports covering medical treatment, drug regimens, caring needs, physiotherapy and recommended follow-up. At discharge the patients received written reports on their medical situation and drug regimens.

Medical assessment and treatment

At admission to the DG all patients were clinically examined by a geriatrician or the resident on call and were screened preoperatively by an extensive battery of blood tests, tests of urine and repeated measurements of pulse, temperature, blood pressure and oxygenation. Chest imaging was performed routinely. Medical assessment to reveal concurrent somatic disorders and optimisation of somatic status was emphasised through treatment of medical disorders, electrolyte disturbances, hypoxemia, anaemia and elevated glucose levels.

Hydration and electrolytes were evaluated regularly during the stay. Fluid intake was measured the first days postoperatively, and intravenous fluid was given until patients were able to drink enough.

Oxygenation was measured regularly; oxygen was supplied if saturation was less than 95%. Blood transfusions were given if $Hb < 10$ g/dl. Monitoring of supine and orthostatic blood pressure was performed. Medication with cardiovascular drugs was adjusted according to these measurements.

To optimise analgesic treatment the nursing staff and physiotherapists assessed pain by using a Verbal Rating Scale (VRS) ranging pain in a scale from one to five during rest and activity [36]. There is no consensus on which opioid should be preferred in frail elderly patients. In DG slow release morphine was the drug of choice; in case of side-effects oxycodone was given instead.

After the urinary catheter was removed on the first postoperative day all patients were scanned with respect to residual urine and checked for infections.

Constipation is very common among hip fracture patients postoperatively. Therefore, preventive treatment with laxatives started the first postoperative day according to a standard procedure. The staff had routines to register defecation of individual patients in order to intensify treatment, especially in patients with cognitive impairment.

Nutrition was in focus both pre-and postoperatively and a specific attention was given to those having a low body mass index, history of recent weight loss or poor appetite. Food intake was monitored if patients were undernourished or had poor appetite. Several patients underwent investigations for pre-fracture weight loss. Many patients were offered specified nutritional drinks until two hours before surgery and protein enriched nutritional drinks and vitamin supplement postoperatively. Meals could be adjusted to each patient's preferences and needs.

The drug regimen was evaluated in all patients. Preoperatively the following drugs were considered to be withdrawn: antihypertensives, diuretics, all drugs with moderate or strong anticholinergic side-effect [39], and drugs with impact on coagulation. Oral antidiabetic drugs were withdrawn and blood glucose was monitored frequently, insulin was given in reduced doses and on demand. Drugs for heart failure, beta-blockers and antiepileptic drugs were continued, while corticosteroids were given in increased doses if adrenal suppression could be suspected. Postoperatively the entire drug regimen was evaluated with respect to indication, dose, side-effects and interactions.

Confusion Assessment Method (CAM) [37] was used for assessment of delirium. The treatment given to the patients in the DG group has been shown to prevent and/or shorten duration of delirium [28]. Use of aids for impaired hearing and/or vision was used regularly. Repeated information to the patients about their medical situation and encouragement of visits by caregivers was considered important. Oxazepam and/or haloperidol (low doses and short duration) were sometimes used for agitation when pharmacotherapy was considered necessary. If an underlying dementia was suspected the general practitioner was recommended to assess the patient on a later occasion.

Many patients had anxiety and were depressed during the hospital stay. This was mainly treated by caring attempts and occasionally by using oxazepam on demand. If anxiety and depression had been a significant problem before the fracture, medical treatment with SSRI or SNRI was sometimes started.

The falls assessment performed during the hospital stay was based upon the case history from patient and caregivers on previous falls and mobility problems, the cause(s) of the present fall and a clinical assessment with focus on comorbid disorders, drugs, muscle strength and balance according to guidelines developed for the DG.

Many patients already received treatment for osteoporosis. If not, a bone mineral density (BMD) measurement was performed in patients with previous fractures or if the hip fracture was a consequence of a low energy trauma. In case of osteoporosis treatment with calcium and vitamin D was given. Treatment with bisphosphonates (orally or

intravenously) was initiated if there were no contraindications and the patient was expected to live long enough to benefit from such treatment.

Ethics

Participation in the trial was voluntary and according to the Helsinki Declaration. Both oral and written information was given at admission to hospital, later during the hospital stay and at follow up assessments. Written informed consent was achieved from all patients preferably before randomization at admission to hospital, but in a few cases 3 to 5 days afterwards. In patients not being able to write, an oral consent was accepted. Proxies were informed about the study if available, this was especially important if the patient was cognitively impaired. The study has been approved by the Regional Committee of Ethics in Medical Research (Mid- Norway) (REK 4.2008.335). Further details have been described in the protocol article [14].

Discussion

The present paper describes the rationale behind, and the development and delivery of a new clinical pathway for treatment of elderly hip fracture patients. As far as we know this is the first randomised clinical trial evaluating a treatment model where elderly hip fracture patients are treated in a DG from admission to discharge. The experimental model focused at CGA, fracture specific treatment and initiation of rehabilitation that was continued after discharge from hospital. Statistical analyses on effect of the intervention will be performed later this year.

In our DG we have long-term experience in performing CGA, the efficacy being shown in a study performed 10 years ago [9]. Since then the CGA process in our DG has continuously improved according to recommendations in the Cochrane review by Ellis et al. [25]. The length of stay has been shortened substantially, as well. In theory, the use of CGA should therefore represent an excellent and effective evaluation and treatment option for frail hip fracture patients.

Benefits in favour of DG can only be shown if patient treatment is better than in the DOS. However, treatment of hip fracture patients was introduced into the DG only four months before study start. The competence on medical treatment of hip fracture patients improved rapidly during this piloting and also during the study period. Orthopaedic surgeons were not routinely engaged in the in-hospital follow-up of patients treated in DG which is a potential weak point. Vice versa there has been a quality improvement in treatment of geriatric patients at our hospital during the last 10 years due to extensive involvement of the DG in teaching at hospital level. This is of course of benefit for geriatric patients in general, but brings uncertainties as to the question on whether the new clinical pathway is sufficiently different from "improved" traditional care.

The intention of the present study was to evaluate if the new model would represent a better in-hospital treatment program. Therefore, to avoid a mix of in-hospital and post-discharge interventions the trial focused on CGA and rehabilitation during the hospital stay with no specific follow-up after discharge. Potential effects of the in-hospital CGA on the primary endpoint of mobility may therefore be lost when measuring for potential benefits 1, 4 and 12 months after discharge.

The Cochrane review by Ellis and co-workers did not show targeting to be essential for outcomes of CGA [25]. Our study population is a case-mix of both healthy and frail participants, although nursing home patients and patients being unable to walk 10 m were excluded due to choice of mobility and place of residence as endpoints. Intuitively we still think that frail hip fracture patients would potentially benefit more from CGA than the non-frail, and that CGA would potentially be beneficial also for patients excluded from the study.

Both the DG and the DOS are treating acutely sick patients and therefore considerably better staffed than for example the ward in Stenvall's study [27]. In our hospital the nursing staff also has to take responsibility for kitchen work and household (except cleaning of floors), thus requiring more nursing staff. The present paper shows that the DG is somewhat better staffed than the DOS. This may of course be explained by an ambitious CGA program. However, other aspects may also have impact i.e. the case-mix in the DG is in general more frail and complex, with almost all patients needing help in ADL, and most of them are cognitively impaired. The DG staff is also extensively involved in supervision and teaching obligations outside the ward and the hospital.

The last follow up sessions in the study are recently finished and the results will reveal if the experimental clinical pathway will be beneficial for both hip fracture patients and society.

Availability and requirements

Project name: the Trondheim Hip Fracture Trial (Clinical Trials Gov NCT00667914)

Project home page: none

Operating system: n.a.

Programming language: n.a.

Other requirements: n.a.

License: n.a.

Any restrictions to use by non-academics: None

Abbreviations

ADL: Activities of Daily Living; ASA: American Society of Anaesthesiologists; CAM: Confusion Assessment Method; CAS: Cumulated Ambulation Score; CGA: Comprehensive Geriatric Assessment; CHS: Compression Hip Screw; DG: Department of Geriatrics; DHS: Dynamic Hip Compression Screw;

DOS: Department of Orthopaedic Surgery; IADL: Instrumental Activities of Daily Living; SPPB: Short Physical Performance Battery; VRS: Verbal Rating Scale.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
IS participated in planning research design and performance of the study, was responsible for making clinical guidelines and is the primary author of this paper. OS initiated the study and has been the project leader; he also led the work on implementing the intervention in the Department of Geriatrics (DG). AP has been participated in planning the study, treating patients in DG, completing data files and will be responsible for analysing the data. EE has been participating in planning and performing the intervention at the DG. JLH has made substantial contribution to plan and perform the study including research design, intervention, completing the data base. LGJ has contributed in teaching and supervising the staff at DG with fracture-related treatment. All authors have contributed to the drafting of this paper and read and approved the final version.

Acknowledgements
The study has been funded by the Norwegian Research Council (NFR grant 186515), the Central Norway Health Authority, the Department of Neuroscience, NTNU, the St. Olav Hospital Trust, the SINTEF and St. Olav Fund for Research and Innovation and the Municipality of Trondheim.
We want to acknowledge the staff at the Department of Geriatrics for their enthusiasm, competence and willingness during the study. We thank the Trauma Unit at the Department of Orthopaedic Surgery and Emergency Department for the participation in a challenging trial during 2 ½ years. Consultant Hans Hynne, Department of Anaesthesiology has given useful information and support during the trial and when preparing the current paper.
Further we want to thank Kristin Taraldsen and Pernille Thingstad, Department of Neuroscience, NTNU for an extensive and impressive work over four years on patient recruitment, study-related follow-up and data collection, and work with data files. We also want to thank Sarah E. Lamb, Clinical Trials Unit, University of Warwick, UK for very important contribution to the research design and conduct of the study.

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Received: 6 March 2012 Accepted: 27 June 2012
Published: 16 July 2012

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doi:10.1186/1756-0500-5-355
Cite this article as: Saltvedt *et al.*: Development and delivery of patient treatment in the Trondheim Hip Fracture Trial. A new geriatric in-hospital pathway for elderly patients with hip fracture. *BMC Research Notes* 2012 **5**:355.

Paper II

Comprehensive geriatric care for patients with hip fractures: a prospective, randomised, controlled trial

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Summary

Background Most patients with hip fractures are characterised by older age (>70 years), frailty, and functional deterioration, and their long-term outcomes are poor with increased costs. We compared the effectiveness and cost-effectiveness of giving these patients comprehensive geriatric care in a dedicated geriatric ward versus the usual orthopaedic care.

Methods We did a prospective, single-centre, randomised, parallel-group, controlled trial. Between April 18, 2008, and Dec 30, 2010, we randomly assigned home-dwelling patients with hip-fractures aged 70 years or older who were able to walk 10 m before their fracture, to either comprehensive geriatric care or orthopaedic care in the emergency department, to achieve the required sample of 400 patients. Randomisation was achieved via a web-based, computer-generated, block method with unknown block sizes. The primary outcome, analysed by intention to treat, was mobility measured with the Short Physical Performance Battery (SPPB) 4 months after surgery for the fracture. The type of treatment was not concealed from the patients or staff delivering the care, and assessors were only partly masked to the treatment during follow-up. This trial is registered with ClinicalTrials.gov, number NCT00667914.

Findings We assessed 1077 patients for eligibility, and excluded 680, mainly for not meeting the inclusion criteria such as living in a nursing home or being aged less than 70 years. Of the remaining patients, we randomly assigned 198 to comprehensive geriatric care and 199 to orthopaedic care. At 4 months, 174 patients remained in the comprehensive geriatric care group and 170 in the orthopaedic care group; the main reason for dropout was death. Mean SPPB scores at 4 months were 5·12 (SE 0·20) for comprehensive geriatric care and 4·38 (SE 0·20) for orthopaedic care (between-group difference 0·74, 95% CI 0·18–1·30, p=0·010).

Interpretation Immediate admission of patients aged 70 years or more with a hip fracture to comprehensive geriatric care in a dedicated ward improved mobility at 4 months, compared with the usual orthopaedic care. The results suggest that the treatment of older patients with hip fractures should be organised as orthogeriatric care.

Funding Norwegian Research Council, Central Norway Regional Health Authority, St Olav Hospital Trust and Fund for Research and Innovation, Liaison Committee between Central Norway Regional Health Authority and the Norwegian University of Science and Technology, the Department of Neuroscience at the Norwegian University of Science and Technology, Foundation for Scientific and Industrial Research at the Norwegian Institute of Technology (SINTEF), and the Municipality of Trondheim.

Introduction

Hip fractures are frequent in older people (>70 years) and represent a worldwide challenge.[1] Because of population ageing, fragility fractures are an increasing burden on health-care systems and societies.[2] Most older people who fracture a hip are frail, have comorbidities, and show a functional deterioration that is typical of geriatric patients.[3] After a fracture, both short-term and long-term outlooks for patients are generally poor, with increased 1 year mortality (18–33%),[4] and negative effects on activities of daily living and mobility. A review of long-term disability in patients with hip-fractures that summarised a weighted average of relevant studies estimates that 42% of survivors do not return to their prefracture mobility, 35% are incapable of walking independently, 20% are unable to shop independently,[5] and about 20% enter a long-term care facility during the first year after a fracture.[6] Hip fractures have substantial socioeconomic effects and large, attributable costs, with acute and post-acute institutional care as the primary driver.[6]

Although surgical care is crucial for improving outcomes after a hip fracture, the proposal that a hip fracture in an older person represents a geriatric rather than an orthopaedic disorder calls for new clinical approaches.[7] Comprehensive geriatric care is an alternative form of care; when practised in dedicated geriatric wards, it improves outcomes for frail older patients who are acutely admitted to hospital, and might be equally relevant for geriatric patients with hip fractures.[8]

Guidelines and recommendations have addressed the importance of combined geriatric and orthopaedic (orthogeriatric) care as an alternative to traditional treatment,[9] although the optimum treatment model is unknown. As summarised in reviews,[10,11] several in-hospital models of orthogeriatric care have been

Lancet 2015; 385: 1623–33

Published Online February 5, 2015 http://dx.doi.org/10.1016/S0140-6736(14)62409-0

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developed, including geriatric consultation teams, comanaged care between geriatricians and orthopaedic surgeons, and a range of interdisciplinary orthogeriatric care pathways. These models have had beneficial effects on delirium, complication rates, and mortality.

Most models of orthogeriatric care reported in the scientific literature are initiated after surgery and undertaken in orthopaedic contexts, and are linked to specific in-hospital and post-discharge rehabilitation programmes[10] A few, non-randomised studies have investigated acute orthogeriatric care pathways for which all assessments and treatments except surgery were done within a geriatric ward by an interdisciplinary team. One of these studies[7] showed important benefits for complication rates, walking ability, and mortality. Investigators from the Oslo Orthogeriatric Trial[12] reported a clinical pathway for patients with a hip fracture, for which the entire assessment and treatment programme, except surgery, took place in an acute geriatric setting; however, no effect was shown on cognition as the primary outcome.

The aim of our trial was to assess the effectiveness of comprehensive geriatric care versus usual orthopaedic care provided throughout an entire hospital stay, with only the fracture assessment and surgical treatment done by orthopaedic surgeons. We investigated both short-term and long-term outcomes in randomly assigned patients, with assessments done at 1, 4, and 12 months after surgery. Because immobility is an immediate result of a fracture and also later contributes to long-term functional deterioration,[5] we chose mobility at 4 months as the primary outcome.

Methods

Study design and participants

We did a prospective, single-centre, randomised, controlled trial at St Olav University Hospital in Trondheim, Norway. St Olav is a central hospital for 300 000 inhabitants of Sør-Trøndelag County, with 25 municipalities and a total area of 18 848 km², and a regional centre for 696 000 inhabitants in mid-Norway. The health-care system in Norway is organised and financed by the public sector, and based on equal access to services irrespective of social or economic status. In Norway, most patients with hip fractures stay in hospital for at least 2 days after surgery. A few patients are discharged directly home, but most are transferred to dedicated rehabilitation facilities or nursing homes for short-term or long-term stays. Services after discharge are, in principle, provided according to needs.

The protocol and intervention programmes for the study have been published previously.[13,14]

All patients admitted to the hospital with hip fractures were screened (briefly, a nurse approached all potentially eligible patients with a confirmed hip fracture in the emergency room, or their next-of-kin). Home-dwelling people aged 70 years or older who had been able to walk 10 m before the fracture were eligible. (Patients living in their homes or sheltered housing, or who were staying temporarily in any kind of institution were defined as home-dwelling.) We excluded patients with pathological fractures, multiple traumas, or a short life expectancy, or who were living permanently in nursing homes or already participating in the investigation. The study was approved by the Regional Committee of Ethics in Medical Research (REK4.2008.335), the Norwegian Social Science Data Services (NSD19109), and the Norwegian Directorate of Health (08/5814). Patients or their next-of-kin gave informed written consent to be included in the study before participation.

Randomisation and masking

Provided eligibility criteria were confirmed, patients were enrolled and randomly assigned in a 1:1 ratio by a nurse to either the orthopaedic ward for orthopaedic care or the geriatric ward for comprehensive geriatric care. Patients were transferred to the allocated wards directly from the emergency department after treatment allocation.

The randomisation sequence was computer-generated in blocks of a size unknown to the investigators. We used a web-based, computer-generated service prepared by the Unit of Applied Clinical Research, Norwegian University of Science and Technology (NTNU).

Masking of the patients and staff delivering the treatment was not possible, and we were only partly able to accomplish masking of assessors during follow-up.

Procedures

The initial diagnosis of a hip fracture was made by an orthopaedic surgeon, who also established the type of operation that was needed. Preoperative and postoperative care was undertaken in the two wards by separate teams. Patients in both groups of the trial received care and physiotherapy in accordance with national and international guidelines.[14] Geriatricians or other doctors with skills in the management of older people did not routinely visit the orthopaedic ward, and orthopaedic specialists did not routinely visit the geriatric ward. By request, for only a few patients, geriatricians briefly assessed patients receiving orthopaedic care; vice versa, the orthopaedic surgeon assessed a few patients receiving comprehensive geriatric care.

The clinical pathway for comprehensive geriatric care (table 1) was organised both before and after the operation as a systematic and interdisciplinary process, with an emphasis on comprehensive medical assessment and treatment, initiation of rehabilitation through mobilisation, and planning of discharge started early. Individualised rehabilitation plans were developed for patients who were discharged directly home. The number of staff members per bed was higher in the comprehensive geriatric care unit than in the orthopaedic care unit (nurses 1·67 *vs* 1·48, doctors 0·13 *vs* 0·11, physiotherapist 0·13 *vs* 0·09, and occupational therapist 0·13 *vs* 0·00). The orthopaedic ward was relocated to a new hospital building on 1 Sept, 2009.

	Comprehensive geriatric care	Orthopaedic care
Department	Department of Geriatrics, Clinic of Internal Medicine	Department of Orthopaedic Surgery, Clinic of Orthopaedics and Rheumatology
Facilities*	Geriatric ward: Five one-bed rooms organised in a group together reserved for patients with hip fractures within a 15-bed ward	Orthopaedic trauma ward: One, two, or four-bed rooms in a 19-bed ward before, or single rooms in a 24-bed ward after relocation Mixed orthopaedic trauma patient population
Team members,†number per bed		
Geriatricians	0·13	..
Registered nurses, licensed practical nurses	1·67	1·48
Physiotherapists	0·13	0·09 (0·07 after relocation)
Occupational therapists	0·13	None
Orthopaedic surgeons	..	0·11 (0·08 after relocation)
Treatment	Structured, systematic interdisciplinary comprehensive geriatric assessment and care focusing on: somatic health (comorbidity management, review of drug regimens, pain, nutrition, elimination, hydration, osteoporosis, and prevention of falls); mental health (depression, delirium); function (mobility, p-ADL and i-ADL) and social situation Early discharge planning Early mobilisation and initiation of rehabilitation	Following of routines of Department of Orthopaedic Surgery

For both groups, management of standard treatment and surgery is the same: standard treatment consists of preoperative intravenous fluid, analgesia (preoperative femoral nerve block, regular paracetamol, opioids on demand), thromboembolic prophylaxis, perioperative antibiotic prophylaxis, use of pressure relieving mattresses to avoid decubitus ulcers, and preoperative assessments by an anaesthetist; surgery consists of spinal anaesthesia, two-screw fixation for non-dislocated femoral neck fractures, hemiarthroplasty for dislocated femoral neck fractures, and a sliding hip screw system for trochanteric and subtrochanteric fractures (some subtrochanteric fractures are fixed with antegrade intramedullary nailing). p-ADL=personal Activities of Daily Living. i-ADL=instrumental Activities of Daily living. *Orthopaedic care was relocated to a new hospital building after 219 of 397 patients were recruited. †Separate teams with no collaboration.

Table 1: **Management in the comprehensive geriatric assessment and care and the orthopaedic care groups**

After discharge from hospital the primary health-care services were responsible for follow-up in both groups, but neither group was routinely offered hospital-based follow-up after discharge. When needed, the orthopaedic surgeon arranged follow-up at the orthopaedic outpatient clinic for patients in both groups. For baseline registration of prefracture comorbidity we used the Charlson comorbidity index. The scores range from 0 to 30, with a high score suggesting high comorbidity.[15] For the preoperative risk classification we used the Acute Physiology And Chronic Health Evaluation II severity of disease classification system (APACHE II), with scores ranging from 5 to 89, high scores suggesting a high risk.[16] The minimum score with APACHE II is 5 points because all patients were aged 70 years or older.

Follow-up assessments were done on day 5 after the operation, and 1, 4, and 12 months after surgery. Assessments were done by assessors who were not associated with patient care. 4 month and 12 month assessments were undertaken at the hospital if possible. These assessments were not linked to medical assessments except for five emergency cases from both groups that were managed by a geriatrician. All 1 month assessments, and 4 month and 12 month assessments in very sick patients, were done wherever the patient resided. Whenever possible during data collection, patients were the primary informant. The exception was for Clinical Dementia Rating scores, which were collected from proxies by telephone for all patients, and scores for the Barthel index and the Nottingham Extended ADL scale, which were collected from proxies by telephone for 10–20% of patients in both groups who were unable to provide the data.

Medical information, including complications, admissions to hospital, and visits to outpatient clinics was obtained from hospital records. Information about admissions to institutional rehabilitation centres was obtained from the Norwegian Patient Registry, visits to family doctors and physiotherapists from the Norwegian Health Economics Administration, and nursing home stays and other primary care services from the municipalities' records (appendix).

For the **Norwegian Patient Registry** see www.npr.no

See **Online** for appendix

Outcomes

The primary outcome was mobility at 4 months after surgery measured by the Short Physical Performance Battery (SPPB),[17] assessing standing balance, walking speed, and ability to rise from a chair, assessed in the intention-to-treat population. The total score ranges from 0–12; high scores suggest better mobility.

Secondary outcomes were mobility assessed by Timed Up and Go (TUG) measured as time in seconds to complete specific actions—a short time suggests better mobility,[18] personal activities of daily living (ADLs) measured by the Barthel Index with a score range of 0–20 (a high score suggests increased independence),[19] instrumental ADLs (i-ADL), measured by the Nottingham Extended ADL scale with a score of 0–66 (a

high score suggests better ability to undertake instrumental i-ADL),[20] cognition assessed with the Clinical Dementia Rating scale scored with a sum of boxes with a range of 0–18 (a low score suggests better cognitive function)[21] and the Mini Mental Status Examination (MMSE) with a score range of 0–30 (a high score suggests better cognition)[22] and quality of life assessed by the EuroQoL-5 dimension-3L (EQ-5D-3L) questionnaire with a score range of –0·594 to 1 (a low score suggests a worse quality of life).[23] Fear of falling was assessed by the Falls Efficacy Scale International-short form (FES-I-s) with a score range of 7–28 points, for which a low score suggests decreased fear,[24] and mood by the Geriatric Depression Scale, ranging from 0 to 15 points, for which a low score suggests a better mood.[25]

Additional outcomes described in the protocol manuscript[13] such as gait control and daily physical activity from the whole set of participants will be published in separate reports. Our choice of this wide range of outcome variables is, to a large extent, in line with published recommendations for studies assessing orthogeriatric comanagement of hip fractures.[26]

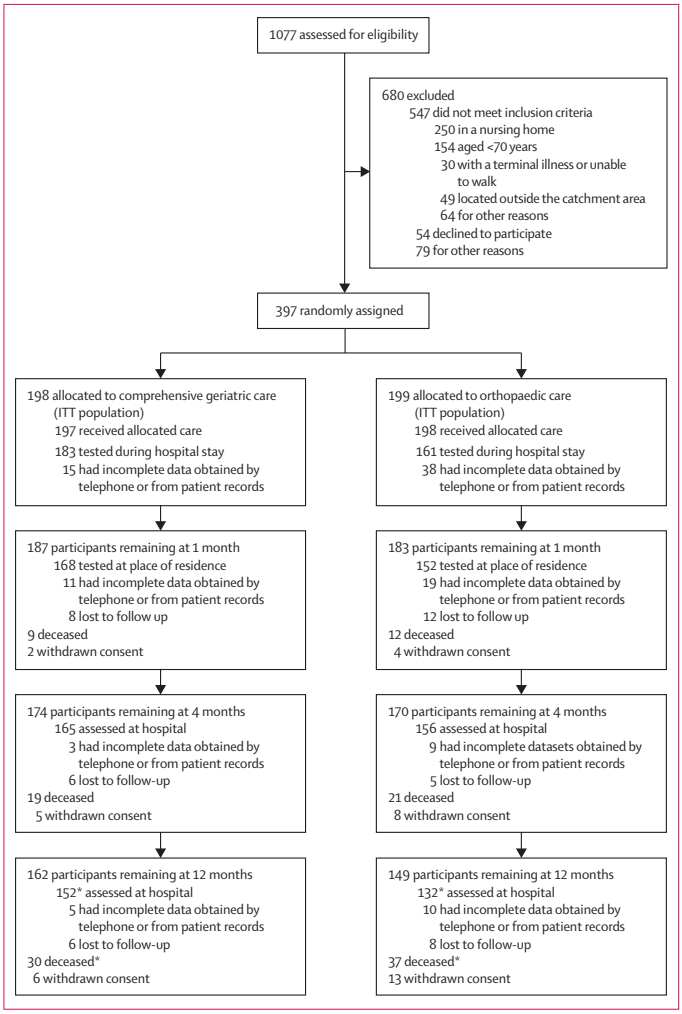

Figure 1: **Trial profile**
*One participant registered as deceased in the comprehensive geriatric care group and one in the orthopaedic care group finished their final tests before death. Data for health-care services and economics were available for all patients except one in the orthopaedic care group who withdrew consent to collect data from registries; therefore n=198 in both groups.

Statistical analysis

Sample size was calculated from an estimated effect size of 1·0 point in mean SPPB score at 4 months after surgery. (1·0 point is regarded as a substantial meaningful change, and 0·5 points is a small meaningful change).[27] We expected a reduction of 10% in participants resulting from death and a 10% dropout because of withdrawals during

	Comprehensive geriatric care (N=198)	Orthopaedic care (N=199)
Age (years)	83·4 (5·4)	83·2 (6·4)
Female	145 (73%)	148 (74%)
Sheltered housing	26 (13%)	20 (10%)
Living alone	115 (58%)	124 (62%)
Barthel Index (0–20)	18·3 (2·3)	18·1 (2·8)
Nottingham Extended ADL scale (0–66)	42·5 (17·7)	41·9 (17·5)
Clinical Dementia Rating Scale (0–18)	2·7 (4·0)	2·7 (3·9)
APACHE II (5–89)	9·3 (3·3)	9·1 (2·9)
Charlson comorbidity index (0–30)	2·3 (2·3)	2·3 (2·0)
Previous diagnoses		
Heart disease	97 (49%)	89 (45%)
Stroke	49 (25%)	57 (29%)
Diabetes	23 (12%)	28 (14%)
Dementia	27 (14%)	26 (13%)
Cancer	53 (27%)	43 (22%)
Kidney disease	18 (9%)	9 (5%)
Fracture type		
Femoral neck	119 (60%)	127 (64%)
Trochanteric	66 (33%)	58 (29%)
Subtrochanteric	13 (7%)	14 (7%)
Surgical treatment		
Hemiarthroplasty	76 (38%)	88 (44%)
Screws	38 (19%)	32 (16%)
Bone plates and screws	69 (35%)	63 (32%)
Other	13 (7%)	14 (7%)
Died before surgery	2 (1%)	2 (1%)

Data are mean (SD) or n (%). ADL=activities of daily living. APACHE II=Acute Physiology And Chronic Health Evaluation disease severity classification II.

Table 2: **Baseline characteristics**

the first 4 months. With an α value of 0·05, 304 patients were needed for 80% power, but 380 patients were needed to allow for an estimated 20% dropout rate. We planned to stop recruiting participants by the end of 2010.

A statistical analysis plan was completed before doing any data analyses. Group allocation was masked during analysis of the primary outcome. All randomly assigned patients who met the inclusion criteria were included in the intention-to-treat population.

An independent clinical trials unit (Warwick Clinical Trials Unit, University of Warwick, Warwick, UK) reviewed emerging safety data (mortality and serious adverse events), and the assumptions underlying the sample-size calculation when 200 patients had been recruited. No planned or unplanned formal interim analyses were undertaken.

We used single imputation with the expectation maximation algorithm for individual missing items on questionnaires and performance tests, with scores from the same timepoint as predictors.

We checked the normality of residuals by visual inspection of Q-Q plots. Results are reported as means, SE, and SD. Linear mixed models for repeated measurements were done with all outcome assessment scales as dependent variables, controlling for age, sex, and femoral neck fractures.[28] We analysed differences in the length of stay in the hospital between groups with linear regression. Differences between groups in the number of patients discharged directly home, admitted to hospital, or staying in nursing homes were analysed with Pearson's χ^2 test.

We assessed the effect of the move of the orthopaedic care unit to new facilities on SPPB, the Barthel index, and the Nottingham Extended ADL scale by use of a linear mixed model with an interaction product of group, before and after the move.

We regarded two-sided p values of less than 0·05 to be deemed statistically significant, and report 95% CIs when relevant.

We assessed cost-effectiveness from a broad health-care perspective. We calculated QALYs with the area-under-the-curve approach, with an assumption of a linear change in EQ-5D-3L values over time.[29] If a patient died, they were classified as having no previous decrease in quality of life. All patients were given an equal EQ-5D-3L baseline score based on a systematic review of osteoporosis-related utility values.[30] The different health states generated from the EQ-5D-3L were assigned values from the UK time-trade-off tariff[23] (ie, each health state was assigned a number between –0·594 and 1·000).

We imputed missing data for the EQ-5D-3L by multiple imputation using age, sex, fracture type, Charlson comorbidity index, APACHE II, the Barthel index, and MMSE as predictors. Imputations were done 100 times.

The sum of surgical treatment costs and length of stay multiplied by the cost per day constituted the cost per index stay, with costs per day for comprehensive geriatric

	Comprehensive geriatric care		Orthopaedic care		Difference	
	N	Mean (SE)	N	Mean (SE)	Estimate (95% CI)	p value
Hospital	198		199			
Mobility						
Short Performance Physical Battery	183	1·61 (0·19)	161	1·04 (0·20)	0·56 (0·20 to 1·10)	0·042
1 month	187		183			
Mobility						
Short Performance Physical Battery	173	3·59 (0·19)	160	3·09 (0·20)	0·50 (–0·05 to 1·05)	0·08
Timed Up and Go	140	31·32 (1·53)	120	32·80 (1·66)	–1·48 (–5·92 to 2·95)	0·51
Cognition						
Mini Mental Status Examination	168	23·43 (0·44)	152	22·40 (0·46)	1·03 (–0·22 to 2·27)	0·11
Activities of daily living						
Barthel Index	179	14·53 (0·28)	169	14·21 (0·29)	0·32 (–0·47 to 1·11)	0·43
Nottingham Extended ADL Scale	179	17·05 (1·25)	169	14·87 (1·29)	2·19 (–1·33 to 5·71)	0·22
Depressive symptoms						
Geriatric Depression Scale	169	4·81 (0·25)	154	4·84 (0·26)	0·03 (–0·74 to 0·68)	0·94
Fear of falling						
Falls Efficacy Scale International-short form	158	12·73 (0·35)	139	13·97 (0·37)	–1·24 (–2·24 to –0·24)	0·015
Quality of life						
EQ–5D–3L	176	0·46 (0·26)	165	0·40 (0·26)	0·05 (–0·02 to 0·12)	0·16
4 months	174		170			
Mobility						
Short Physical Performance Battery	165	5·12 (0·20)	160	4·38 (0·20)	0·74 (0·18 to 1·30)	0·010
Timed Up and Go	153	24·05 (1·47)	136	25·94 (1·56)	–1·90 (–6·09 to 2·31)	0·38
Cognition						
Clinical Dementia Rating scale	159	3·59 (0·35)	145	4·38 (0·36)	–0·79 (–1·70 to 0·20)	0·12
Mini Mental Status Examination	165	23·92 (0·44)	156	22·83 (0·46)	1·10 (–0·15 to 2·34)	0·08
Activities of daily living						
Barthel index	168	16·31 (0·29)	165	15·30 (0·29)	1·01 (0·21 to 1·81)	0·013
Nottingham Extended ADL Scale	168	33·59 (1·29)	164	27·42 (1·31)	6·17 (2·57 to 9·78)	0·001
Depressive symptoms						
Geriatric Depression Scale	165	4·32 (0·25)	155	4·75 (0·26)	–0·42 (–1·14 to 2·90)	0·24
Fear of falling						
Falls Efficacy Scale International—short form	154	11·31 (0·35)	144	12·57 (0·37)	–1·27 (–2·27 to –0·27)	0·013
Quality of life						
EQ–5D–3L	177	0·54 (0·26)	170	0·46 (0·26)	0·08 (0·01 to 0·15)	0·033

(Table 3 continues on next page)

	Comprehensive geriatric care		Orthopaedic care		Difference	
	N	Mean (SE)	N	Mean (SE)	Estimate (95% CI)	p value
(Continued from previous page)						
12 months	162		149			
Mobility						
Short Physical Performance Battery	151	5·30 (0·21)	133	4·61 (0·22)	0·69 (0·10 to 1·28)	0·023
Timed Up and Go	139	21·93 (1·54)	117	23·25 (1·68)	−1·32 (−5·79 to 3·15)	0·56
Cognition						
Clinical Dementia Rating scale	152	4·00 (0·36)	138	4·59 (0·37)	−0·59 (−1·59 to 0·41)	0·25
Mini Mental Status Examination	152	24·13 (0·46)	132	22·69 (0·49)	1·44 (0·12 to 2·77)	0·033
Activities of daily living						
Barthel Index	158	16·46 (0·29)	142	15·33 (0·30)	1·13 (0·31 to 1·96)	0·007
Nottingham Extended ADL Scale	158	35·20 (1·33)	142	28·81 (1·41)	6·39 (2·59 to 10·19)	0·001
Depressive symptoms						
Geriatric Depression Scale	151	4·10 (0·26)	131	4·82 (0·27)	−0·72 (−1·46 to 0·02)	0·06
Fear of falling						
Falls Efficacy Scale International-short form	149	10·81 (0·36)	119	12·03 (0·39)	−1·21 (−2·24 to −0·18)	0·021
Quality of life						
EuroQol-5d-3L	176	0·52 (0·22)	161	0·45 (0·23)	0·09 (0·02 to 0·16)	0·015
QALY 0–12 months	198	0·49 (0·02)	199	0·42 (0·02)	0·07 (0·01 to 0·13)	0·019

ADL=activities of daily living. QALY=quality-adjusted life-years.

Table 3: **Clinical assessments**

care and orthopaedic care calculated on the basis of differences in staff numbers. Patient use of services after discharge was combined with unit costs to calculate the cost per patient (appendix).

We evaluated cost-effectiveness by calculating the difference in mean costs and dividing by the difference in mean QALYs, assuming a theoretical threshold of €62 500 per QALY gained. We estimated any uncertainty about the incremental cost-effectiveness ratio (ICER) by bootstrapping the costs and effects 1000 times.[31]

Any patient who died during the course of the trial was allotted zero costs and zero health from the date of death and was not classified as censored.[32] We did all analyses with the IBM SPSS statistics 20.0 program.

This trial is registered with ClinicalTrials.gov, number NCT00667914.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analyses, or data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients were recruited from April 18, 2008, to December 30, 2010 (the prespecified finishing timepoint). 1077 patients were screened for eligibility, of whom 397 were randomly assigned to receive either comprehensive geriatric care (n=198) or orthopaedic care (n=199) (figure 1). Most patients were randomly assigned in the emergency room before they were transferred to their assigned ward. 22 were randomly assigned in the orthopaedic ward within 24 h of

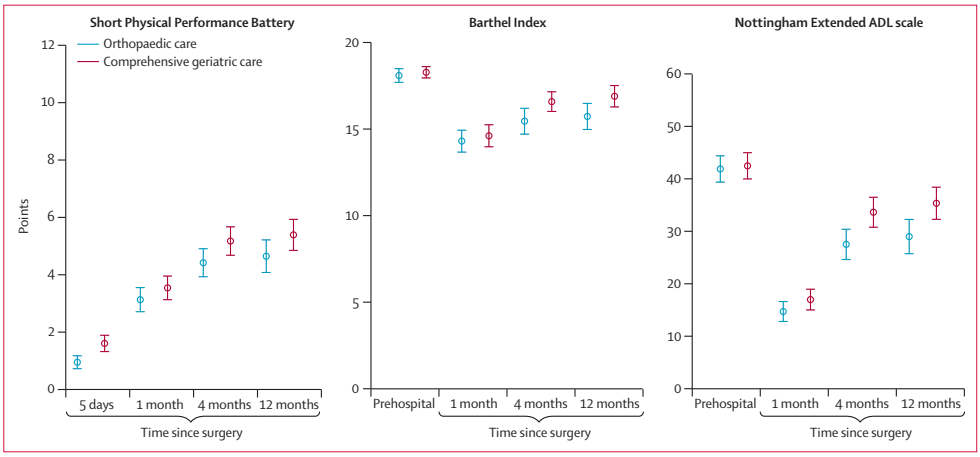

Figure 2: **Mobility, activities of daily living, and instrumental activities of daily living**
Data are mean, 95% CI. ADL=activities of daily living.

admission; ten of these were randomly assigned to comprehensive geriatric care and moved to the geriatric ward after surgery. The most common reason for ineligibility was that the patient resided permanently in a nursing home (250 [46%] of 547) or was too young (aged <70 years; 154 [28%] of 547). At 12 months, only 33 patients (8%) had withdrawn or were registered with missing data (lost to follow-up) and we noted no significant differences between the groups for withdrawn patients or missing data (p=0·14, 95% CI –8·70 to 3·70).

Baseline characteristics did not differ between the groups (table 2). For the 397 randomly assigned patients, the mean age was 83 years (SD 6·1), 293 (73%) were women, and 239 (60%) lived alone before the fracture. The proportion of patients with femoral neck fractures did not differ between groups (table 2). Mortality in the comprehensive geriatric care and orthopaedic groups at 12 months was 30 (15%) of 198 and 37 (18%) of 199 patients, respectively (p=0·36). We noted no differences in fracture-related or other complications during the index stay (data not shown). Mean prefracture personal-ADL Barthel index scores were 18·3 (SD 2·3) and 18·1 (2·8), and mean prefracture Nottingham Extended ADL scale scores were 42·5 (17·7) and 41·9 (17·5).

For the primary outcome of mobility at 4 months, the comprehensive geriatric care group had better mean SPPB scores than the orthopaedic care group, with a between-group difference of 0·74 points (95% CI 0·18–1·30, p=0·010; table 3, figure 2). The between-group difference at 12 months was 0·69 (0·10–1·28; p=0·023). 165 patients in the comprehensive geriatric care group and 160 in the orthopaedic care group were assessed for the primary outcome. Between-group differences in mean SPPB scores were in favour of comprehensive geriatric care on day 5 after the operation but were not significant at 1 month (table 3, figure 2). We noted no significant between-group differences for mobility TUG during follow-up (table 3).

The mean instrumental ADL score during the study was significantly better in the comprehensive geriatric care group than in the orthopaedic care group at 4 months and at 12 months (table 3). Mean p-ADL score at 4 and 12 months after surgery also favoured comprehensive geriatric care. Quality-of-life measures were higher in the comprehensive geriatric care group than in the orthopaedic care group; however, the difference at 1 month was not significant (table 3, appendix).

Cognitive function assessed by the MMSE at 4 months and the Clinical Dementia Rating Scale at any timepoint did not differ significantly between the groups (table 3). However, MMSE scores were better for comprehensive geriatric care at 12 months than for orthopaedic care (table 3).

Fear of falling was reduced in the comprehensive geriatric care group compared with the orthopaedic care group at 1 month, 4 months, and 12 months. We noted no significant between-group differences in symptoms of depression as measured by the Geriatric Depression Scale (table 3).

The mean preoperative waiting times were similar between groups; however, mean length of hospital stay was significantly longer in the comprehensive geriatric care group than in the orthopaedic care group (table 4). A significantly higher proportion of patients in the comprehensive geriatric care group was discharged directly home than in the orthopaedic care group

	Comprehensive geriatric care	Orthopaedic care	Difference	
			Estimate (95% CI)	p value
Preoperative waiting-time (h)	28·7 (26·1)	29·3 (20·6)	−0·6 (−5·3 to 4·1)	0·80
Length of stay (days)	12·6 (0·43)	11·0 (0·54)	1·7 (0·20 to2·93)	0·025
Discharged directly home	47 (25%)	20 (11%)	13·9 (6·3 to 21·4)	0·001
Number of patients living at home				
1 month after treatment	171 (91%)	161 (87%)	3·9 (−2·5 to 10·4)	0·23
4 months after treatment	154 (86%)	141 (80%)	6·4 (−1·5 to 14·2)	0·14
12 months after treatment	140 (83%)	122 (76%)	7·6 (−1·2 to 16·2)	0·09
Patients admitted to hospital				
0–4 months after treatment	55 (29%)	58 (31%)	−2·2 (−11·4 to 7·0)	0·64
4–12 months after treatment	54 (30%)	66 (37%)	−7·1 (−16·7 to 2·7)	0·16
Rehabilitation				
0–4 months after treatment	121 (63%)	135 (72%)	−8·8 (−18·0 to 0·6)	0·07
4–12 months after treatment	13 (7%)	19 (11%)	−3·5 (−9·7 to 2·5)	0·25
Short-term stay in a nursing home				
0–4 months after treatment	44 (23%)	51 (27%)	−4·2 (−12·9 to 4·5)	0·34
4–12 months after treatment	17 (10%)	30 (17%)	−7·5 (−14·6 to −0·4)	0·038
Permanent stay in a nursing home				
0–4 months after treatment	28 (15%)	32 (17%)	−2·5 (−9·9 to 5·0)	0·51
4–12 months after treatment	36 (20%)	45 (25%)	−5·3 (−14·0 to 3·4)	0·22

Number included in the analyses for comprehensive geriatric care versus orthopaedic care: index stay 198 versus 198; discharge home 191 versus 187; place of residence at 1 month 188 versus 185, at 4 months 179 versus 177, at 12 months 168 versus 161; use of care after the index stay: 0–4 months 191 versus 187, 4–12 months 179 versus 177.

Table 4: **Health-care use**

	Comprehensive geriatric care (n=198)	Orthopaedic care (n=198)	Difference	
	Mean (SD)	Mean (SD)	Estimate (95% CI)	p value
Index stay	11 868 (4185)	9537 (4 393)	2331 (1483 to 3178)	<0·0001
Hospital costs after discharge	7 745 (15 006)	11 022 (20 119)	−3277 (−6784 to 230)	0·07
Rehabilitation stay	8 105 (9076)	9633 (11 125)	−1529 (−3535 to 477)	0·14
Nursing home stay	14 874 (30 153)	18 798 (32 959)	−3923 (−10 164 to 2318)	0·22
Other primary health and care services	11 741 (15 128)	10 496 (14 498)	1246 (−1683 to 4173)	0·40
Total cost	54 332 (38 048)	59 486 (44 301)	−5154 (−13 311 to 3007)	0·22

Costs are in euros for 2010.

Table 5: **Cost per patient**

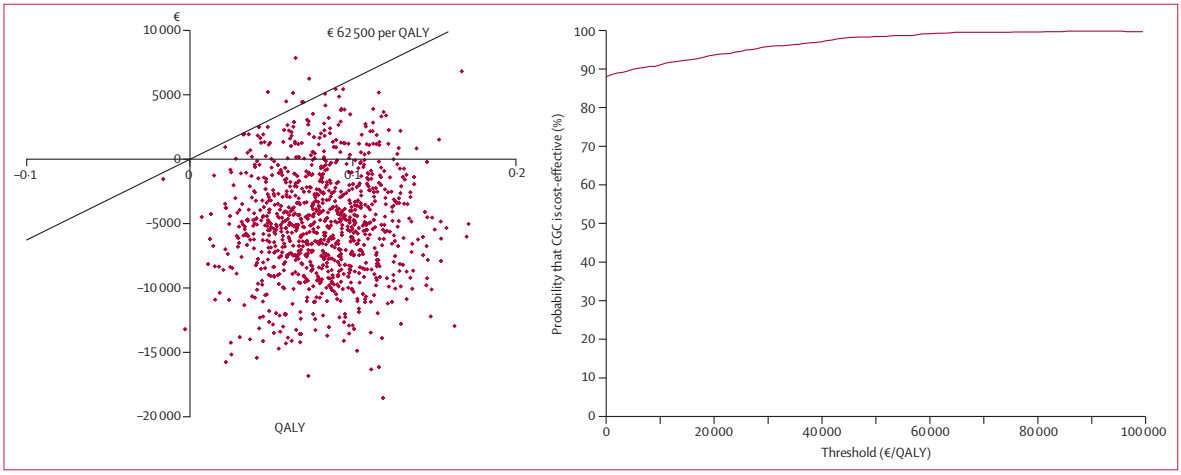

Figure 3: **Cost per QALY analysis**
The figure shows the cost-effectiveness plane and acceptability curve. CGC=comprehensive geriatric care. QALY=quality-adjusted life-years.

(table 4). Fewer patients receiving comprehensive geriatric care were admitted to short-term nursing home stays between 4 and 12 months after surgery than patients receiving orthopaedic care. Differences between groups in the proportions of patients living at home, or admitted to hospital or long-term nursing homes during follow-up were not significant (table 4).

The comprehensive geriatric care index stay was more costly than the orthopaedic care stay, with a mean difference of €2331 (95% CI 1483–3178), p<0·0001. Differences between the groups for total costs per patient were non-significant (mean €–5154 [–13 311 to 3007], p=0·22). Table 5 and appendix show further details about costs for other health services.

The number of QALYs was higher in the comprehensive geriatric care group than in the orthopaedic care group at 4 and 12 months (table 3).

The ICER was calculated to €–71751 per QALY gained. Bootstrap results suggest that comprehensive geriatric care has a 99% probability of being cost effective compared with orthopaedic care, with the assumption of a threshold of €62 500 per QALY gained. Comprehensive geriatric care has an 88% probability of being both less costly and more effective than orthopaedic care—ie, of being a dominant alternative (figure 3).

At the time that the orthopaedic care group relocated to a new hospital, 219 (55%) of 397 patients had been recruited. The interaction analyses of the effect of the orthopaedic care group moving to new facilities during the study period did not show significance at the 0·05 level for mobility (SPPB scores, p=0·078), personal ADLs (Barthel index scores, p=0·13), or instrumental-ADLs (Nottingham Extended ADL scale scores, p=0·19).

Discussion

We investigated if any benefit was gained when patients with a hip fracture receive all assessments and treatments except surgery in an acute geriatric ward from an interdisciplinary team, rather than the usual orthopaedic care ward. For the primary outcome of mobility as measured by SPPB 4 months after surgery, the results were better with comprehensive geriatric care than with traditional orthopaedic care (see appendix for details). Most secondary outcomes were also better with comprehensive geriatric care than with orthopaedic care, including mobility and cognition at 12 months, activities of daily living, fear of falling, and quality of life at 4 and 12 months. The length of stay was significantly longer in the comprehensive geriatric care group, and significantly more patients in this group were discharged directly home, than were patients in the orthopaedic care group. Differences in the place of residence, and the number of patients admitted to hospital, rehabilitation, or long-term nursing-home care during 1 year of follow-up did not differ between groups, except for fewer patients in the comprehensive geriatric care group admitted for short-term stays in a nursing home 4–12 months after surgery than those in the comprehensive geriatric group. The analyses suggest a high probability of comprehensive geriatric care being both less costly and more effective than orthopaedic care for patients aged 70 years or older.

Mobility was chosen as the primary outcome because immobility is an immediate result of a fracture, and older patients with hip fractures often have a marked and permanent deterioration in their walking ability.[5] SPPB is regarded as an objective outcome of physical performance, and also captures the health status of the participant.[33] Therefore the significant SPPB

between-group difference of 0·74 at 4 months, regarded as a clinically meaningful change,[27] and long-term improvement of mobility with comprehensive geriatric care, represent important findings. This result is consistent with the orthogeriatric study of Shyu and colleagues[34] done in an acute orthopaedic context (panel). Results from subgroup analyses in the Oslo Orthogeriatric trial[12] done in a geriatric context also indicated improved mobility with comprehensive geriatric care for home-dwelling patients. We noted, however, no between-group differences for the secondary mobility outcome of TUG. It seems that the TUG is less sensitive to change than the SPPB, possibly because patients who are unable to undertake this test are not given a score.

The significant and clinically meaningful benefits[35] of comprehensive geriatric care for instrumental-ADLs at 4 and 12 months have not been shown in previous studies of patients with hip fractures. The ability to complete instrumental-ADLs is an important need for independent living. In line with previous rehabilitation studies[10] and results from the trial by Shyu and colleagues,[34] we showed a slight effect on ability to undertake personal-ADLs in favour of the comprehensive geriatric care group. The magnitude of the differences in quality of life at 4 and 12 months is roughly the mean of reported minimally important differences, which further supports the results of ADL benefits for the comprehensive geriatric care group.[36] The 1·44 point difference in mean MMSE scores at 12 months can be regarded as clinically significant at a group level in these frail, older patients, although a difference of 3 points is needed to be of clinical importance for individual patients with dementia.[37] We noted a significant and probably clinically important 1·2 point difference in FES-I-s scores at 1, 4, and 12 months in favour of the comprehensive geriatric care group.[38]

The proportion of patients discharged directly home was significantly higher in the group receiving comprehensive geriatric care than in the group assigned to orthopaedic care. This finding could be attributed to a better in-hospital programme for discharge planning and mobilisation. On one hand, the notion of a better mobility programme in the comprehensive geriatric care group during the hospital stay is supported by patients spending more time in a standing position and walking in the comprehensive geriatric care group than the orthopaedic care group, as measured by use of body-worn sensors on day 4 after surgery.[39] On the other hand, length of stay in the hospital was significantly increased in the group receiving comprehensive geriatric care, compared with the group receiving orthopaedic care. These findings contrast with previous studies of orthogeriatric care, as summarised in a review.[10] In our study context, periods of heightened need for trauma-ward beds in the orthopaedic care department might have increased the rate of discharge for this group. Another explanation for the discharge policy could be that comprehensive geriatric care and discharge planning are time-consuming. Also, some extra days in hospital might have been sufficient for some patients to have been discharged directly home.

Costs separated by service categories show that the index stay was more costly in the comprehensive geriatric care group than in the orthopaedic care group; between-group differences of costs for later hospital stays, stays in rehabilitation facilities and nursing

***Panel:* Research in context**

Systematic review

We searched the PubMed database, with no date restrictions, for English-language studies of orthogeriatric treatment models of hip fractures, especially new models focusing on long-term results of acute comprehensive geriatric assessment and care practised in geriatric wards. The search included studies with or without randomisation, reviews, and meta-analyses.

We started the search on Feb 17, 2007, during the planning of the study and repeated it several times until Dec 15, 2013. The search terms were "hip fracture" combined with either "orthogeriatric" or "comprehensive geriatric assessment". The last search identified 69 and 42 reports, respectively, of which we manually searched reference lists to identify relevant publications not found by the primary search. We excluded studies of long-term, in-hospital rehabilitation, events within an orthogeriatric environment that were not related to the treatment itself, consultation services after discharge, and rehabilitation were excluded.

We found two reviews[10,11] describing an update of the scientific literature on orthogeriatric treatment of hip-fracture patients in various service contexts. We identified only one randomised trial focusing on both an acute care setting and a short-term comprehensive geriatric care programme investigating long-term effects on mobility and function.[34] However, this model was run in an orthopaedic context including specific elements of rehabilitation both in-hospital and after discharge.

Other publications presented protocols without results and some reported results from non-randomised trials. One such large study from Israel compared acute treatment of hip-fracture patients in a geriatric ward as compared with treatment in an orthopaedic ward and reported impressive short-term and long-term results in favour of the geriatric pathway. This study was the origin of our model.[7] However, several limitations make the reliability of results from this kind of study questionable, the most important being related to the non-randomised design. A model similar to ours has been studied in the Oslo Orthogeriatric trial.[12] Although no effect on cognition was shown, subgroup analyses from this trial suggested improved mobility in the comprehensive geriatric care group.

Interpretation

Our trial showed that patients aged 70 years or more with hip fractures have significant and clinically important improvements in mobility, activities of daily living, and quality of life when they receive comprehensive geriatric assessment and care in a specialised orthogeriatric unit, compared with usual care on an orthopaedic trauma ward. Comprehensive geriatric care is also more cost effective than orthopaedic care. The strengths of the study were the size, the controlled design, and the care of the participants, and the main limitations are the absence of masking and the single-centre location.

To our knowledge this is the first time such an effect has been shown in a large, prospective, randomised, controlled trial. Our results are in accordance with findings from previous non-randomised studies of hip fractures and studies of acutely sick, frail, older patients without hip fractures, for which comprehensive geriatric assessment and care were implemented in dedicated geriatric wards.

homes, and costs for health-care services at home were not significant. The combined effect of differences in costs, mortality, and quality of life as captured by the ICER, shows that comprehensive geriatric care is a cost-effective alternative to orthopaedic care. To our knowledge, the cost-effectiveness of comprehensive geriatric care has not been reported in previous trials of orthogeriatric comanaged care in patients with hip fractures, although it has been shown in a non-randomised investigation.[40]

The major strengths of our study are the randomised controlled design with the control group receiving usual orthopaedic care, the large sample size, the high retention rate, the focus on long-term functional outcomes and cost-effectiveness, and that our primary outcome measure was a detailed, performance-based test[17,27] rather than the self-reported measures often used in previous studies.[5] Analyses were done according to a prespecified statistical analysis plan and treatment allocation was masked during the first data analysis.

The main study limitation is related to masking and concealment of the treatment allocation. Masking of the patients and staff delivering the treatment was not possible, and we were only partly able to accomplish masking of assessors during follow-up. The absence of masking might potentially have affected results from performance-based tests and questionnaires. However, data collection for discharge destination, place of residence, and use of health-care services was undertaken with the group allocation concealed. The results on these outcomes and also the activity monitoring data assessed on day 4 after the surgery[39] support our results for the primary outcome. Therefore, despite the absence of masking, we argue that our results are robust.

Important limitations for the analysis of cost-effectiveness include the absence of baseline EQ-5D-3L measurements, making it impossible to control for any potential imbalances in baseline values.[41] Data for costs were obtained from registries, which avoids any difficulties with recall and selection bias, but might be affected by incorrect coding or absence of registration. The economic evaluation is based on secondary outcomes; however, this trial was not powered adequately enough to show differences in costs.

Our study was a single-centre trial, which also raises the important question of generalisability and feasibility. Comprehensive geriatric care is a multifaceted, integrated assessment and treatment involving several people from different professions and backgrounds. Treatment effects are therefore not likely to result from the competence and skills of one person. The work was undertaken in a large hospital, with national and international guidelines applied by the Department of Orthopaedic Surgery. Thus, the treatment in the orthopaedic care group should be similar to such treatment in many other hospitals in northern Europe. Furthermore, our study sample was large, and representative of home-dwelling, older patients with a hip-fracture and preserved walking ability, and constituted 397 (75%) of all 530 screened patients with hip fractures that were eligible. Patients were mainly excluded because they were too young and not regarded as in need of comprehensive geriatric care, or they were staying permanently in nursing homes and excluded because of the choice of primary and secondary outcomes. Furthermore, our results are supported by results from previous studies of orthogeriatric hip-fracture treatment,[10,11] and also by results from studies of comprehensive geriatric care in frail, older patients in general.[8] Accordingly, we think that our results are valid and that comprehensive geriatric care is feasible in other settings, although only multicentre studies can support this hypothesis.

This is the first trial to show benefit and cost-effectiveness when patients aged 70 years or older with hip fractures are admitted directly to a geriatric ward for comprehensive geriatric care. Existing guidelines suggest that treatment of older patients with fragility fractures should be organised as orthogeriatric care.[9] The present study supports these recommendations for older patients with hip fractures, and shows that preoperative and postoperative orthogeriatric management of these patients improves outcomes for 4 months, and for at least 1 year after surgery, compared with treatment in traditional orthopaedic trauma wards.

Contributors

OS conceived the idea for the study and managed the project. OS, IS, JLH, PT, AP, and SEL designed the study. PT, KT, AP, TS, GH, and VH acquired and managed the data. SL and SEL supervised the statistical analyses, and AP, GH, and SL did the analyses. AP wrote the statistical analysis plan. VH, GH, TS, and LGJ were responsible for the health economics part of the study. AP, GH, IS, OS, and JLH wrote the final report. All authors interpreted the data and contributed to revisions of the report

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was funded by the Norwegian Research Council, the Central Norway Health Authority, the St Olav Hospital Trust, the Department of Neuroscience at the Norwegian University of Science and Technology, the Foundation for Scientific and Industrial Research at the Norwegian Institute of Technology (SINTEF) and St Olav Hospital Fund for Research and Innovation, and the Municipality of Trondheim. The funding sources had no effect on the analyses, interpretation, or presentation of the data. SEL received support from the Oxford NIHR Musculoskeletal Biomedical Research Unit, Nuffield Orthopaedic Centre, University of Oxford and from the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care Oxford at Oxford Health NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. We thank the study participants for their contributions to the study. We also thank the staff in the geriatric ward in the Department of Geriatrics for their willingness and enthusiasm and the Department of Orthopaedic Surgery for the collaboration during the investigation. We thank Thorlene Egerton for useful comments on the final draft of the manuscript, and Liv Faksvåg Hektoen for management of data obtained from municipality records. We also acknowledge taxi driver Torbjørn Lie for his assistance during the trial.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Prestmo A, Hagen G, Sletvold O, et al. Comprehensive geriatric care for patients with hip fractures: a prospective, randomised, controlled trial. *Lancet* 2015; published online Feb 5. http://dx.doi.org/10.1016/S0140-6736(14)62409-0.

Supplementary appendix to the article

A randomised trial of comprehensive geriatric care in hip-fracture patients

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Perspective and time horizon

The economic evaluation was conducted from a broad health care perspective**.** In keeping with the outcome analyses from the main paper, a twelve months perspective was applied in the cost utility analysis.

Health services and cost parameters

Health and social care services, for which patient utilisation data have been collected, are listed in Table A1, together with the corresponding unit costs. Patient service utilisation data was combined with unit costs to calculate cost per patient. Services received after the index stay (post discharge), were aggregated into four main categories: hospital care, institutional rehabilitation, nursing home, and other primary health and social care services.

Published unit costs were used if available; otherwise we used information from local experts and municipal web-sites to establish unit cost. References are listed in Table A1. All cost values are presented in 2010 Euro (EUR). The average exchange rate in 2010 was eight Norwegian kroner (NOK) to one EUR.[1]

The unit cost of the index stay was calculated as the sum of surgical treatment cost and length of stay (LOS) multiplied by per diem cost. Surgical treatment cost was assumed equal across groups and calculated based on published data.[2] The cost per diem of care in the orthogeriatric and the orthopaedic ward was calculated separately on the basis of staff level differences[3] and wage cost information from the hospital accounting system multiplied by an over-head. The staff category specific wage costs per full time equivalent were equal across Comprehensive Geriatric Care (CGC) and Orthopaedic Care (OC), with staff category levels as the only difference. Staff level per patient in CGC and OC groups respectively were: nurses 1·67/1·48, medical doctors 0·13/0·11, physiotherapists 0·13/0·09 and occupational therapists 0·13/0·00.[3]

The unit cost for institutional rehabilitation was gathered from the municipality and private care providers. The costs of nursing home services are calculated by using average per diem costs for these services, as they are reported to Statistics Norway. Other primary health and social care services include home nursing care, hour-based rehabilitation, home care services, safety alarm, meals-on-wheels, visits to daycentre and GP services, for which published unit costs were applied, except for safety alarm and meals-on-wheels.

Service utilisation data

Use of resources is shown in Table A2. All information concerning the index stay was collected from St Olav Hospital's patient administrative system. Post discharge hospital service utilisation data was collected from St Olav Hospital's patient administrative system and institutional rehabilitation data from the Norwegian Patient Register, with supplementary information from the municipal patient records. Nursing home utilisation data and information on resource consumption of primary health and social care services were collected from municipal patient records, with two exceptions: visits to general practitioners (GPs) and visits to physiotherapist were collected from the Norwegian Health Economics Administration. There was no missing data on the use of resources except for one patient who withdrew consent for further collection of data during hospital treatment.

Health outcomes and missing data

Patients completed the EQ-5D-3L at one, four and 12 months, but no baseline measurements were collected because the patients were admitted as emergencies and with severely deteriorated health state. Instead all patients were given an equal base line score, 0·268, gathered from a systematic review of osteoporosis related utility values.[4] Number of missing units, *i.e.* whole EQ-5D-3L questionnaires of remaining participants, were 50/391 (12·8%), 37/384 (9·6%) and 41/378 (10·8%) at the one, four and 12 months respectively. Missing data

on the EQ-5D-3L (whole questionnaires) were imputed by multiple imputations in 100 imputed data sets. The imputation model included EQ-5D-3L index values at the three time points, age, gender, fracture type, treatment group, Charlson Comorbidity Index, APACHE 2 measured at baseline, and the clinical outcome variables Barthel Index and the Mini Mental Status Examination. The imputation model was restricted to predict values inside the possible range, *i.e.* values between -0·594 and 1 for the EQ-5D-3L. The results are described in Figure A1.

When scoring the EQ-5D-3L we used the UK TTO tariff.[5] Quality adjusted life years (QALYs) were calculated using the area under the curve approach,[6] assuming a linear change in EQ-5D-3L values between time points. Patients who died were assumed to have the last measured EQ-5D-3L value until death.

Evaluation of cost effectiveness

Cost effectiveness was evaluated by calculating the difference in mean costs divided by the difference in mean QALYs; the incremental cost effectiveness ratios (ICER). A theoretical threshold of EUR 62500 per QALY formed the basis for cost-effectiveness evaluation. This threshold is currently under debate in Norway.

Uncertainty in the ICER was estimated by means of bootstrapping, due to the skewed costs and effects data, and the challenges related to calculating a confidence interval around a ratio. [7]

1000 samples were drawn randomly from the sample of costs and effects, with replacement, to build an empirical non-parametric estimate of the uncertainty in the ICER. The 1000 recalculated ICERs were plotted on the cost-effectiveness plane and the percentage of simulated ICERs falling below the assumed limit was calculated.[7, 8]

Patients' deceases during the course of the trial were allotted zero costs and zero health from the date of dying, but were not considered censored.[9, 10]

One way sensitivity analyses

We assessed the robustness of the findings by sensitivity analyses. Unit costs for post discharge hospital stay (cost per diem) were set equal to CGC index stay unit costs, while unit costs for nursing home stay and unit cost of rehabilitation stay were decreased by 25%. Both separate and simultaneous analyses were performed. All analyses showed only minor changes in mean total cost difference between CGC and OC and did not alter conclusions, *c.f.* Table A3.

Table A1 Unit costs in 2010 EUR

Main service categories	Services type	Type of unit	Unit cost	Source of information
Hospital care :				
Index stay	CGC ward	Days	685	Saltvedt et al. 2012[3] and hospital accounting system
	OC ward	Days	573	Saltvedt et al. 2012[3] and hospital accounting system
	Surgery	Operation	3231	Frihagen et al. 2010[2]
Post discharge	Hospital stay	Days	1254	Norwegian Directorate of Health, average cost per diem[11]
	Outpatient visits	Visits	150	Vossius et al.2013[12]
Institutional rehabilitation	Rehabilitation stay	Days	371	Municipality, private providers of care
Nursing home	Short and long term stay	Days	288	State-Municipality-reporting[13]
Other primary health and social care services	Home nursing care	Hours	72	Vossius et al. 2013[12]
	Hour based rehabilitation	Hours	71	Hektoen et al. 2009[14]
	Home care services	Hours	47	Vossius et al. 2013[12]
	Safety alarm	Days	2	Municipal websites/local experts
	Meals on wheels	Meals	10	Municipal websites/local experts
	Visits to daycentre	Visits	109	Vossius et al. 2013[12]
	General practitioner (GP)	Visits	54	GP tariff[15] and Norwegian guidelines for economic evaluation in healthcare[16]

CGC – Comprehensive Geriatric, Care OC – Orthopaedic care

Table A2 Use of resources

			Comprehensive geriatric care (n=198)		Orthopaedic care (n=198†)		Difference		
Main category	**Service type**	**Units**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Estimate**	**Confidence interval**	**p-value**
Hospital care									
Index stay	Hospital stay	Days	12·61	(6·11)	11·01	(7·67)	1·60	(0·23 to 2·97)	0·025
Post discharge	Hospital stay	Days	5·63	(11·76)	8·35	(15·9)	-2·72	(-5·48 to 0·04)	0·053
	Outpatient visits	Visits	4·58	(11·40)	3·68	(5·17)	0·90	(-0·85 to 2·65)	0·31
Institutional rehabilitation	Rehabilitation stays	Days	21·82	(24·44)	25·94	(29·96)	-4·12	(-9·52 to 1·29)	0·14
Nursing home stays	Short and long term stays	Days	51·74	(104·88)	65·38	(114·64)	-13·65	(-35·36 to 8·06)	0·22
Total time in institutions	All stays	Days	91·78	(110·49)	110·68	(121·36)	-18·33	(-41·26 to -4·60)	0·12
Other health and social care services	Home nursing care	Hours	22·75	(50·73)	19·33	(40·54)	3·42	(-5·65 to 12·49)	0·46
	Hour based rehabilitation	Hours	29·04	(58·51)	24·95	(56·99)	4·09	(-7·33 to15·50)	0·48
	Home care services	Hours	103·91	(168·83)	63·70	(130·38)	39·50	(9·72 to 69·28)	0·0095
	Safety alarm	Days	163·26	(157·73)	147·03	(152 ·98)	16·24	(-14·46 to 46·94)	0·30
	Meals on wheels	Meals	36·57	(93·34)	43·38	(103·49)	-6·81	(-26·28 to 12·66)	0·49
	Visits to daycentre	Visits	18·38	(64·21)	29·21	(80·81)	-10·83	(-25·25 to 3·59)	0·14
	GP consultations	Visits	15·67	(13·85)	14·14	(12·03)	1·53	(-1·03 to 4·09)	0·24

GP- General Practitioner

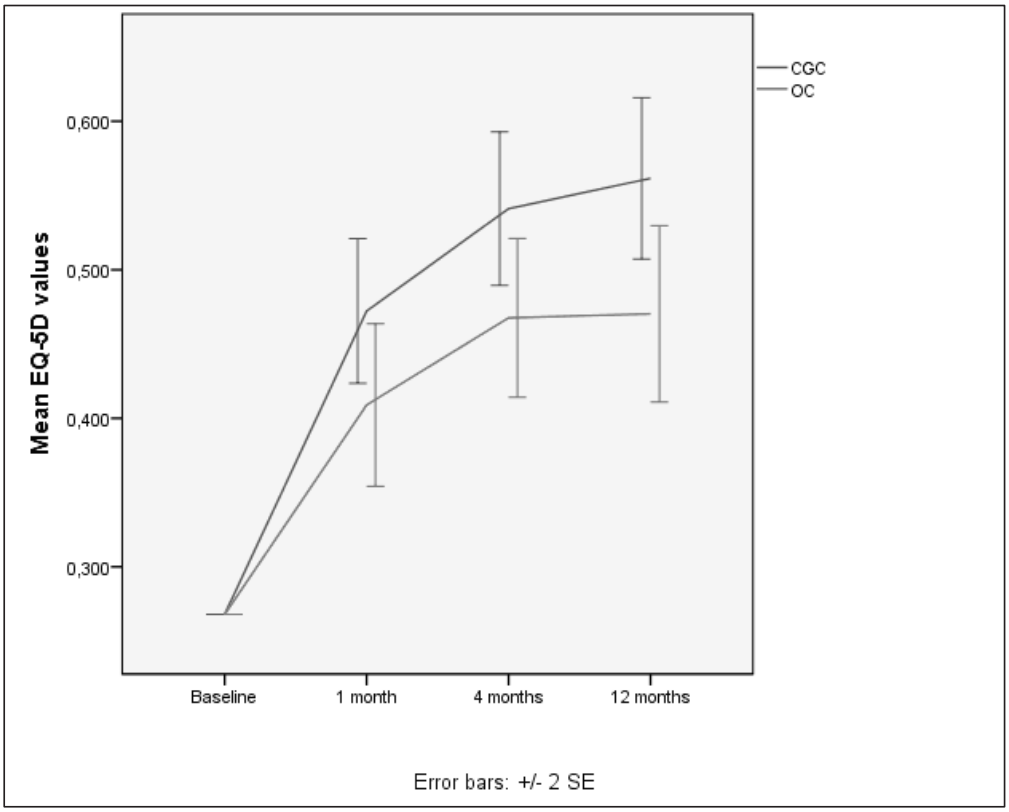
†- One patient withdrew consent before collecting any data for evaluation of cost-effectiveness

Table A3 One way sensitivity analysis on selected parameters

	Base case				Sensitivity			
Parameter	**Value of parameter**	**Total cost CGC**	**Total cost OC**	**Difference CGC-OC**	**Value of parameter**	**Total cost CGC**	**Total cost OC**	**Difference CGC-OC**
Unit cost post discharge hospital stay	1 254	54 332	59 486	-5 154	609	50 704	54 102	-3 398
Unit cost nursing home stay	288	54 332	59 486	-5 154	245	52 135	56 707	-4 572
Unit cost rehabilitation stay	371	54 332	59 486	-5 154	318	53 168	58 101	-4 933
All changes above simultaneously	As above	54332	59 486	-5 154	As above	47 340	49 939	-2 599

CGC – Comprehensive Geriatric, Care OC – Orthopaedic care

Figure A1 Mean EQ-5D-3L values. Baseline values are based on published literature.[4]



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Paper III

Who benefits from orthogeriatric treatment? Results from the Trondheim Hip-Fracture Trial

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Funding: Norwegian Research Council, Central Norway Regional Health Authority, St Olav Hospital Trust and Fund for Research and Innovation, Liaison Committee between Central Norway Regional Health Authority and the Norwegian University of Science and Technology, the Department of Neuroscience at the Norwegian University of Science and Technology, Foundation for Scientific and Industrial Research at the Norwegian Institute of Technology (SINTEF), and the Municipality of Trondheim.

Keywords: geriatric assessment, hip fracture, orthogeriatric, sub group

Abstract

Background: In The Trondheim Hip Fracture Trial patients treated with comprehensive geriatric care (CGC) in a geriatric ward had better mobility, and personal and instrumental ADL (p-and i-ADL) than patients receiving traditional orthopaedic care (OC). In this study we investigate whether the effect of CGC depended on age (over/under 80 years), gender, fracture type (intra-capsular (ICF)/extra-capsular (ECF)), or pre-fracture i-ADL.

Methods: Home-dwelling hip fracture patients ≥70 years were randomised to receive CGC (n=198) or OC (n=199). Mobility was measured by Short Physical Performance Battery (SPPB), p-ADL by Barthel Index (BI), i-ADL by Nottingham Extended ADL scale (NEAS), cognition by Mini-Mental Status Examination (MMSE). Data were analysed by linear mixed models with interactions (treatment, time, and subgroup).

Results:

Within-group differences: At four and/or 12 months CGC patients with ICF, pre-fracture NEAS ≥45, females, independent of age had better scores for SPPB and NEAS. CGC was superior to OC for men with better MMSE scores at 12 months, for ECF patients with better NEAS scores at 12 months, and for patients with pre-fracture NEAS <45 on NEAS at four months.

Between-group differences: CGC was significantly better for patients <80 years on NEAS at four months, for ICF on BI at four and 12 and SPPB at 12 months, and with pre-fracture NEAS >45 on NEAS at 12 months.

Conclusions: The benefits of CGC were more pronounced in patients with ICF and high pre-fracture i-ADL. The results should be used to tailor CGC treatment for hip fracture patients.

ClinicalTrials.gov registration number: NCT00667914.

Background/Introduction

Hip fractures are common with more than 1.3 million fractures annually world wide [1]. A hip fracture represents a major burden both for the individual patient and the society [2], and results in reduced survival, impaired function and problems with independent living. Older age is associated with not regaining basic mobility following a hip fracture. After a hip fracture mortality is higher among men. However, there are conflicting results on gender differences in the regaining of function [3, 4], while several studies have reported that risk of reduced mobility after a fracture is higher in patients with low pre-fracture mobility and in those with extra-capsular fractures (ECF) [5, 6].

Geriatric patients and hip fracture patients share features such as high age, comorbidities, functional limitations, and frailty [7]. Therefore, orthogeriatric treatment models where geriatricians and orthopaedic surgeons collaborate have been developed. As summarised in literature reviews, orthogeriatric treatment models have shown reduction of delirium, post-surgery complication rates and mortality [8, 9], and improved mobility [10]. A recent paper from The Trondheim Hip Fracture Trial reported that treatment of home-dwelling hip-fracture patients with comprehensive geriatric care (CGC) throughout the entire hospital stay gave statistically significant and clinically meaningful better mobility, personal activities of daily living (p-ADL), instrumental ADL (i-ADL), and cognition, and was also cost-effective as compared to traditional care [11].

Previous studies indicate beneficial effects of comprehensive geriatric care (CGC) for hip-fracture patients in general [11, 12], but less is known about benefits of CGC in targeted subgroups. Although a number of prognostic factors for functional outcomes are relatively well known, we have not found any randomised controlled trial (RCT) evaluating treatment effects of CGC versus traditional orthopaedic care (OC) related to subgroup characteristics.

When planning for The Trondheim Hip-Fracture Trial, we hypothesised that benefits of a comprehensive and individualised orthogeriatric treatment programme were independent of age, gender and fracture type, and that focusing functional recovery in the CGC group would especially benefit those with more severe pre-fracture impairments.

The aim of the present study is to explore *post hoc* if treatment effects of CGC as compared to OC depend on subgroups defined by age, gender, type of fracture or pre-fracture function. This will be studied separately for the outcome measures of mobility, p-ADL, i-ADL, and cognition.

Methods

Trial design and patients

The Trondheim Hip-fracture Trial is a prospective RCT performed at St. Olav University Hospital in Trondheim, Norway between April 2008 and January 2012. The protocol, the intervention and clinical outcomes from the study have been published previously [11, 13-15]. Patients were randomised in the emergency room to receive CGC or OC and were transferred to the allocated wards directly after randomisation. Home-dwelling patients 70 years or older who had been able to walk 10 meters prior to the hip-fracture were eligible. Patients with pathological fractures, multiple trauma, short life expectancy, living permanently in a nursing home, or already participating in the study were excluded.

Treatment

As described previously [14] patients in both groups received the same perioperative treatment. In most patients surgery was performed in spinal anaesthesia. Arthroplasty was used for dislocated ICFs (Garden type 3 or 4) while Garden type 1 or 2 fractures were mainly treated with a two-screw fixation. A sliding hip screw system was used for ECF except for some sub trochanteric fractures that were treated with intramedullary nailing. Most patients were allowed full weight bearing postoperatively. In the orthopaedic trauma ward OC patients received treatment according to national and international guidelines. In the geriatric ward patients were treated pre- and postoperatively using CGC performed as a multidimensional interdisciplinary diagnostic process focusing on the patients' medical, mental, social and functional situation. We developed an integrated plan for treatment and follow-up for each patient [14]. The CGC used a broad geriatric scope focusing on medical assessment including review of drug regimen, pain relief, hydration, nutrition, elimination, and assessment of fall risk and osteoporosis. In addition the interdisciplinary team focused on early mobilisation and rehabilitation and early individualised discharge planning.

The primary health care services were responsible for follow-up after discharge from hospital in both groups. Neither group was routinely offered hospital-based follow-up, except for selected patients who were offered follow-up in the orthopaedic outpatient clinic as decided by the orthopaedic surgeons.

Measurements

P-ADL and i-ADL before the fracture and at four and 12 months were assessed by the Barthel Index (BI; 0 to 20 points; 20 best score) and the Nottingham Extended ADL Scale (NEAS; 0 to 66 points; 66 best score) [16, 17]. The median pre-fracture NEAS score was 45, and patients with NEAS scores ≥45 before the fracture were regarded "well-functioning", while those with scores < 45 were regarded "functionally impaired". Data were obtained by interviewing the patient or, if he/she was not able to respond, their next of kin. Mobility at four and 12 months was assessed by the Short Physical Performance Battery (SPPB; 0 to 12 points; 12 best score) [18]. Cognition was assessed by the Mini Mental Status Examination (MMSE; 0 to 30 points; 30 best score) [19]. The American Society of Anaesthesiologists (ASA) score [20] was used as preoperative risk score for mortality. Medical information was collected from hospital records.

Statistical analysis

Differences between subgroups were analysed by linear mixed models with interactions between treatment, time, and subgroup, using SPPB, BI, NEAS, and MMSE as dependent variables. Independent variables were time, group allocation (CGC vs OC), and age (70 to 79 vs ≥80 years), gender, fracture type (ICF vs ECF) and pre-fracture function (median NEAS< 45 vs ≥45). An interaction between the subgroup and the treatment effect implies a three-way interaction (between time, treatment and subgroup). The magnitude of the three-way interaction is not of practical interest, but the interest lies in the effect of treatment group at four and 12 months. Hence, at each time point, we report the treatment effect within subgroups, and the difference in treatment effect between subgroups.

The results within and between subgroups are presented as mean scores for differences with 95% Confidence Intervals (CI). Differences in treatment effect between subgroups are reported with CIs and p-values for the relevant two-way interactions. Two-sided p-values <0.05 were considered statistically significant. For evaluation

of whether test score differences are clinically meaningful previously reported reference values were used: SPPB ≥ 0.5 points [21], BI ≥ 1.49 points [22], NEAS ≥ 2.4 points) [23], and MMSE ≥ 2 points [24]. Analyses were performed using SPSS 21.

Ethics

The study was approved by the Regional Committee of Ethics in Medical Research (REK4.2008.335), the Norwegian Social Science Data Services (NSD19109) and the Norwegian Directorate of Health (08/5814). ClinicalTrials.Gov registry number was NCT00667914.

Results

Baseline characteristics

The CGC and the OC were comparable regarding baseline characteristics (Table 1). Mean age was 83 years, three of four patients were female, and 60% were living alone. More than 50% in both groups had an ASA score of 3 or higher. About 60 % had ICF, of whom 76 (63.9%) in the CGC and 89 (69.3%) in the OC were operated with arthroplasty (Table 1).

Clinically meaningful treatment effects of CGC versus OC within subgroups

Table 2 and Figure 1 show that at four months patients aged 70-79 years treated with CGC had better performance on SPPB, BI and NEAS than patients treated with OC, and at 12 months better performance on NEAS and MMSE. CGC patients' ≥80 years of age had better SPPB scores at four and 12 months, and better NEAS score at 12 months than the OC patients.

In females there were clinically meaningful treatment effects in favour of CGC for SPPB and NEAS at four and 12 months. For men the MMSE scores for the CGC group was better at 12 months, but there were no other statistically significant differences at four or 12 months.

At four and 12 months patients with ICF treated with CGC had better scores on SPPB, BI and NEAS. Patients with ECF had a better treatment effect of CGC than OC only for NEAS at 12 months.

CGC patients with pre-fracture NEAS ≥45 had better scores on SPPB and NEAS at four and 12 months and better MMSE scores at 12 months. Among patients with pre-fracture NEAS <45 there was no statistically significant differences between the CGC and OC group in functional outcomes at four and 12 months.

Clinically meaningful treatment effects of CGC versus OC between subgroups

The analysis showed that CGC was better than OC for patients 70-79 years of age as compared to patients ≥80 years for NEAS at four months, while there were no differences at 12 months. In patients with ICF as compared to ECF, CGC was better for BI at four and 12 months and for SPPB at 12 months. In patients with pre-fracture NEAS ≥45 as compared to NEAS < 45, CGC was better for NEAS at 12 months.

Discussion

We have previously reported that treating home-dwelling hip-fracture patients in an orthogeriatric ward improves mobility, p-ADL, i-ADL and cognition more than treating patients in an orthopaedic ward. Our overall aim of the present study was to explore treatment effects on functional measures between subgroups of the hip-fracture population. This *post hoc* study have shown that home-dwelling hip-fracture patients irrespective of age, gender, type of fracture or pre-fracture function have better effect of CGC than OC in one or more functional outcomes, and that these group differences are of clinical importance. Nevertheless, the results demonstrated only minor differences in functional outcomes between the CGC and OC group among men, patients with ECF, and those with impaired i-ADL before the fracture. Interaction analyses showed that at four months CGC was statistically significantly better for patients < 80 years of age regarding impact on i-ADL, and for ICF patients on p-ADL. At 12 months, CGC was superior in patients with ICF for mobility and p-ADL, and for well-functioning patients regarding i-ADL.

We have not found other publications studying if effects of orthogeriatric care differ in subgroups of patients. However, our overall results indicating somewhat better effects of CGC than OC irrespective of subgroup are in line with a Cochrane review on comparison of comprehensive geriatric assessment with general medical care in hospitalised acutely sick elderly patients, that showed that the benefits were related to treatment in a geriatric ward *per se* and not a consequence of admission criteria like age and other factors [25].

Previous studies have shown that older patients have poorer functional recovery than younger patients after hip-fractures [26]. In the present study there were statistically and/or clinically meaningful differences between the CGC and OC groups independent of age group. For patients ≥ 80 years the effect of CGC was more pronounced at 12 months. The between-subgroup analysis showed a significant effect of CGC on NEAS at four months in patients 70-79 years as compared to patients' ≥80. This difference between age groups disappears after one year where the superior effect of CGC is fairly similar regardless of age. The change is mainly due to improved NEAS in the older group by CGC but not in OC. Our interpretation is that patients ≥80 need more time to improve, and that the effect of CGC may persist beyond discharge due to a better definition of treatment goals, better discharge planning or a better individual plan for rehabilitation.

Arinzon & al [27] have previously found that both men and women improve mobility during hip-fracture rehabilitation, while other studies have found better prognosis for female hip-fracture patients [28]. In our study we found that while female CGC patients had statistically and clinically significant better mobility and i-ADL at four and 12 months, the only effect for male CGC patients was on cognition at 12 months. Still, there was no significant effect of gender in the between-group analyses, possibly due to lack of statistical power. Further research particularly designed to assess gender effects of rehabilitation is warranted in order to improve treatment outcomes particularly in male hip-fracture patients.

Better effect in favour of CGC on the ICF group was found at both four and 12 months, while for the ECF group there was only a rather small effect on i-ADL at four and 12 months. The interaction analyses confirmed these findings by revealing increased benefit of CGC versus OC on several outcomes for ICF as compared to ECF patients. Our findings also support previous studies showing that in general ECF patients have poorer prognosis than ICF patients [29]. One explanation may be that these patients are older, have a larger trauma with more soft tissue damage and needing more extensive surgery. Further research is needed in order to improve the outcome for this patient group.

At four months patients with pre-fracture NEAS score ≥45 showed superior effect of CGC only on p-ADL (BI), while CGC was favourable for i-ADL (NEAS) at 12 months. When planning the study we hypothesised that

patients being "well functioning" before the fracture would benefit least from CGC, while we actually found greatest benefits for this group. However, the median NEAS score was only 45 at baseline, indicating that most participants actually had a functional decline before the fracture. Thus, our findings support previous studies reporting that impaired pre-fracture function appears to be a consistent predictor of unfavourable outcomes and not regaining mobility in older persons with hip-fractures. [5, 6, 26, 29, 30] Since NEAS may be less sensitive to changes among patients with functional decline, the results should be interpreted cautiously.

The strengths of the study are the randomised controlled design and large sample size, and that we had a plan for analysis of subgroup effects based on pre-fracture function before the study started. The main weakness is the *post-hoc* design with choice of remaining subgroups based upon literature review (defined after the main outcomes of the study were known). We have found no consensus on how to categorise patients with impaired function before the fracture, and we therefore dichotomised variables by the median of the baseline i-ADL (NEAS) scores in order to give most power for the analysis. Other weaknesses are lack of power for some subgroups, and that a large number of analyses have been performed increasing the chance of Type I error. The outcome measures in this study were chosen to represent aspects of function, while subjective reported outcomes as for example quality of life were not studied. Thus, conclusions should not be generalised to other domains. The study was exploratory, and further studies primarily designed to study effect of treatment on subgroups have to be undertaken to confirm findings.

Our main results were that in home-dwelling hip-fracture patients all subgroups of patients benefit of CGC on one or more functions (mobility, i- and p-ADL, and cognition), irrespective of age, gender, type of fracture and pre-fracture function. These findings support the implementation of CGC for different subgroups of home-dwelling hip-fracture patients. Our results also show that there is need of further research, especially on ECF, of males, and patients with functional decline before the fracture, where our results indicate a limited value of CGC.

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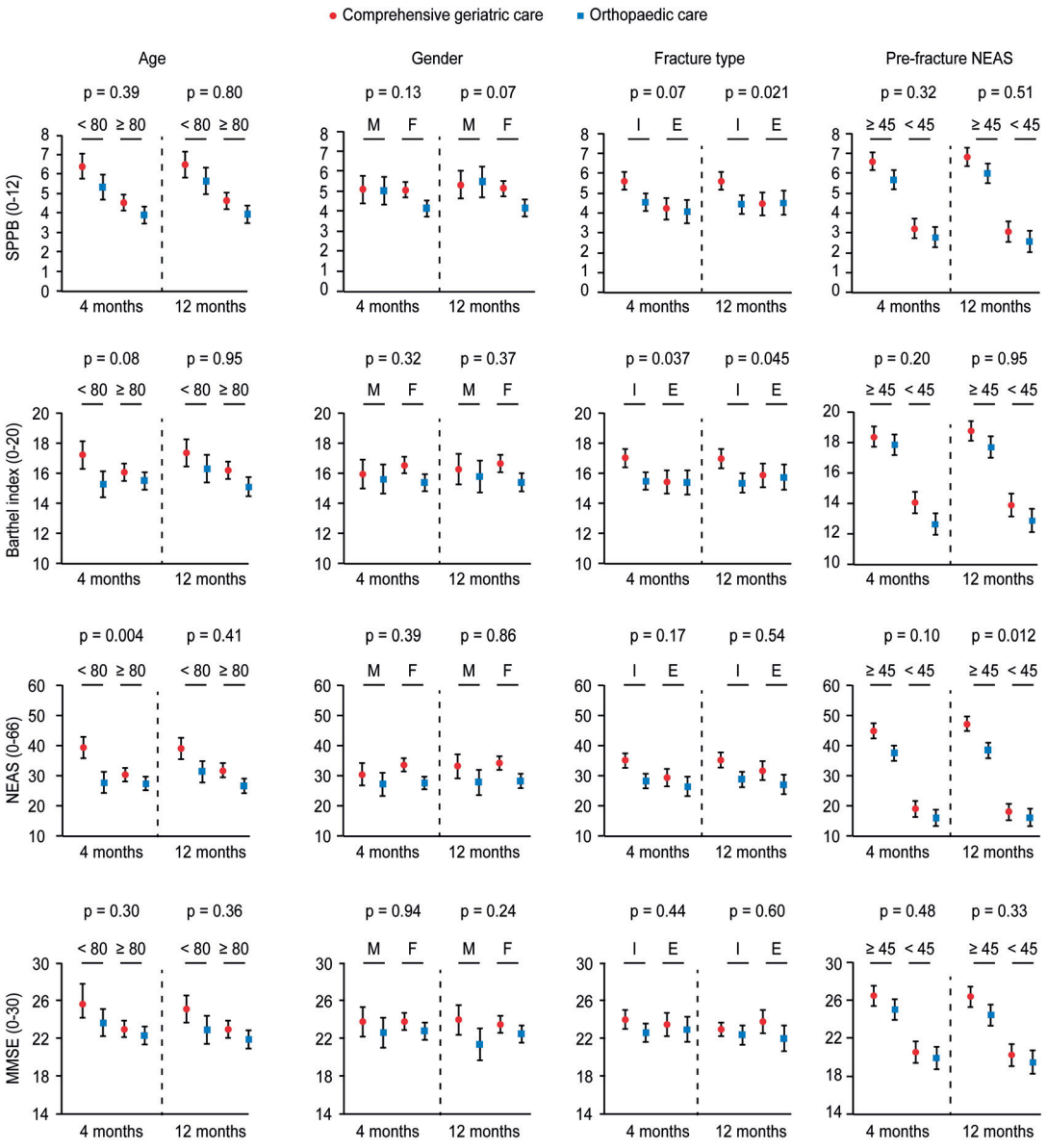

SPPB (0-12) – Short Physcial Performance Battery
NEAS (0-66) – Nottingham Extended ADL Scale
MMSE (0-30) – Mini Mental Status Examination

I – Intra capsular fracture
E – Extra capsular fracture

F – Female
M – Male

Table 1: Baseline characteristics

	Geriatric n= 198		Orthopaedic n= 199	
Age (years) - mean (SD)	83.4	(5.4)	83.2	(6.4)
Sex (female) - n (%)	145	(73.2)	148	(74.4)
Sheltered housing - n (%)	26	(13.5)	20	(10.3)
Living alone - n (%)	115	(58.1)	124	(62.3)
Barthel Index (0-20) - mean (SD)	18.3	(2.3)	18.1	(2.8)
Nottingham Extended ADL Scale (0-66) - mean (SD)	42.5	(17.7)	41.9	(17.5)
ASA (1-5) mean(SD)	2.5	(0.7)	2.6	(0.7)
ASA (1-5) – n (%)				
1 or 2 – healthy or mild systemic disease	89	(45.0)	82	(41.2)
3- severe systemic disease	103	(52.0)	106	(53.3)
4 or 5 - severe systemic disease or moribund	6	(3.0)	11	(5.5)
Previous diagnoses n(%)†				
Heart disease -	97	(49.0)	89	(44.7)
Stroke -	49	(24.7)	57	(28.6)
Diabetes –	23	(11.6)	28	(14.1)
Dementia -	27	(13.6)	26	(13.1)
Cancer -	53	(26.8)	43	(21.6)
Kidney disease -	18	(9.1)	9	(4.5)
Fracture type n(%)				
Femoral neck -	119	(60.1)	127	(63.8)
Extra capsular fracture-	79	(39.9)	72	(36.1)
Surgery n(%)				
Hemi prosthesis -	76	(38.4)	88†	(44.2)
Bone plates and -screws -	69	(34.8)	63	(31.7)
Screws –	38	(19.2)	32	(16.1)
Other††-	15	(7.6)	16	(8.0)

† from the hospital records.

†† Including patients treated with combinations of surgery or no surgery at all due to death.

	Allocation		Difference			Allocation		Difference			2-way interaction		
	Geriatric (Mean)	Orthopaedic (Mean)	GD	(95% CI)	p-value	Geriatric (mean)	Orthopaedic (mean)	GD	(95% CI)	p-value	GD	(95% CI)	p-value
4 months n=357													
	Age 70-79 (n=108)					**Age 80 or older (n=249)**							
SPPB	6.41	5.32	1.09	(0.19 to 1.99)	0.017	4.53	3.91	0.62	(0.03 to 1.20)	0.039	0.47	(-0.60 to 1.55)	0.39
Barthel	17.19	15.27	1.92	(0.66 to 3.18)	0.003	16.05	15.49	0.56	(-0.26 to 1.37)	0.18	1.36	(-0.14 to 2.86)	0.08
NEAS	39.18	27.73	11.44	(6.54 to 16.35)	<0.0001	30.30	27.36	2.94	(-0.25 to 6.13)	0.07	8.50	(2.65 to 14.35)	0.004
MMSE	25.64	23.66	1.97	(-0.06 to 4.02)	0.06	23.02	22.33	0.70	(-0.62 to 2.02)	0.30	1.28	(-1.14 to 3.71)	0.30
	Male (n= 82)					**Female (n=275)**							
SPPB	5.09	5.03	0.06	(-0.93 to 1.05)	0.91	5.07	4.14	0.94	(0.37 to 1.50)	0.001	0.88	(-0.26 to 2.02)	0.13
Barthel	15.94	15.60	0.34	(-1.03 to 1.72)	0.63	16.51	15.36	1.15	(0.36 to 1.94)	0.005	0.81	(-0.78 to 2.40)	0.32
NEAS	30.43	27.13	3.30	(-2.08 to 8.68)	0.23	33.60	27.58	6.02	(2.93 to 9.12)	0.0001	2.72	(-3.48 to 8.93)	0.39
MMSE	23.75	22.64	1.11	(-1.13 to 3.34)	0.33	23.79	22.78	1.01	(-0.27 to 2.29)	0.12	0.09	(-2.48 to 2.67)	0.94
	Intra-capsular fracture (n=221)					**Extra-Capsular fracture (n=136)**							
SPPB	5.61	4.54	1.07	(0.46 to 1.69)	0.001	4.21	4.07	0.14	(-0.66 to 0.94)	0.73	0.93	(-0.08 to1.95)	0.07
Barthel	17.00	15.47	1.53	(0.66 to 2.39)	0.001	15.40	15.38	0.02	(-1.10 to 1.14)	0.97	1.51	(0.09 to 2.92)	0.037
NEAS	35.02	28.16	6.85	(3.48 to 10.23)	0.0001	29.35	26.40	2.94	(-1.45 to 7.34)	0.19	3.91	(-1.64 to 9.45)	0.17
MMSE	24.01	22.62	1.39	(-0.01 to 2.80)	0.05	23.47	22.97	0.50	(-1.30 to 2.30)	0.59	0.90	(-1.39 to 3.19)	0.44
	Pre-fracture NEAS ≥ 45 (n=193)					**Pre-fracture NEAS < 45 (n=164)**							
SPPB	6.59	5.66	0.93	(0.28 to 1.59)	0.005	3.22	2.78	0.45	(-0.26 to 1.15)	0.22	0.49	(0.48 to 1.45)	0.32
Barthel	18.36	17.83	0.53	(-0.40 to 1.47)	0.27	14.06	12.64	1.42	(0.42 to 2.42)	0.005	0.89	(-0.48 to 2.26)	0.20
NEAS	44.77	37.44	7.34	(3.83 to 10.84)	<0.0001	19.06	16.03	3.03	(-0.73 to 6.78)	0.11	4.31	(-0.82 to 9.45)	0.10

MMSE	26.44	25.01	1.43	(-0.08 to 2.94)	0.06	20.51	19.88	0.62	(-1.01 to 2.25)	0.45	0.80	(-1.42 to 3.03)	0.48
12 months n=330													
	Age 70-79 (n=102)					**Age 80 or older (n=228)**							
SPPB	6.48	5.64	0.84	(-0.09 to 1.78)	0.08	4.63	3.93	0.70	(0.08 to 1.31)	0.027	0.14	(-0.98 to 1.26)	0.80
Barthel	17.34	16.29	1.05	(-0.24 to 2.35)	0.11	16.20	15.09	1.11	(0.26 to 1.95)	0.011	0.05	(-1.49 to 1.60)	0.95
NEAS	39.01	31.33	7.68	(2.62 to 12.64)	0.003	31.75	26.63	5.12	(1.79 to 8.45)	0.003	2.56	(-3.50 to 8.62)	0.41
MMSE	25.13	22.90	2.23	(0.16 to 4.30)	0.035	23.00	21.92	1.07	(-0.27 to 2.42)	0.12	1.16	(-1.31 to 3.63)	0.36
	Male (n= 69)					**Female (n=261)**							
SPPB	5.33	5.47	-0.14	(-1.20 to 0.91)	0.79	5.13	4.17	0.96	(0.37 to 1.55)	0.001	1.10	(-0.11 to2.31)	0.07
Barthel	16.25	15.78	0.47	(-0.99 to 1.93)	0.53	16.62	15.38	1.24	(0.42 to 2.06)	0.003	0.77	(-0.90 to 2.44)	0.37
NEAS	33.07	27.78	5.29	(-0.47 to 11.04)	0.07	34.10	28.21	5.89	(2.69 to 9.08)	0.0003	0.60	(-5.98 to 7.19)	0.86
MMSE	23.95	21.36	2.59	(0.30 to 4.87)	0.027	23.50	22.49	1.01	(-0.29 to 2.31)	0.13	1.58	(-1.05 to 4.01)	0.24
	Intra-capsular fracture (n=202)					**Extra-Capsular fracture (n=128)**							
SPPB	5.61	4.42	1.19	(0.54 to 1.84)	0.0003	4.45	4.51	-0.06	(-0.090 to 0.78)	0.89	1.25	(0.19 to 2.31)	0.021
Barthel	16.95	15.33	1.62	(0.72 to 2.52)	0.0004	15.85	15.72	0.13	(-1.02 to 1.27)	0.83	1.49	(0.04 to 2.95)	0.045
NEAS	35.15	28.76	6.40	(2.86 to 9.83)	0.0004	31.66	27.05	4.61	(0.11 to 9.11)	0.045	1.79	(-3.94 to 7.51)	0.54
MMSE	22.94	22.37	1.14	(-0.29 to 2.58)	0.12	23.77	22.00	1.77	(-0.06 to 3.61)	0.06	0.63	(-1.70 to 2.96)	0.60
	Pre-fracture NEAS $\geq$ 45 (n=187)					**Pre-fracture NEAS < 45 (n=143)**							
SPPB	6.81	5.98	0.83	(0.16 to 1.51)	0.016	3.06	2.57	0.49	(-0.26 to 1.24)	0.20	0.34	(-0.67 to 1.35)	0.51
Barthel	18.74	17.68	1.05	(0.10 to 2.01)	0.031	13.89	12.88	1.01	(-0.04 to 2.06)	0.06	0.05	(-1.37 to 1.47)	0.95
NEAS	47.11	38.38	8.73	(5.14 to 12.32)	<0.0001	18.08	16.18	1.90	(-2.06 to 5.85)	0.35	6.83	(1.48 to 12.17)	0.012
MMSE	26.33	24.42	1.91	(0.38 to 3.44)	0.015	20.24	19.47	0.77	(-0.91 to 2.45)	0.37	1.14	(-1.14 to3.41)	0.33

GD – Group difference. SPPB- Short Physcial Performance Battery. Barthel – Barthel Index. NEAS – Nottingham Extended ADL Scale. MMSE- Mini Mental Status Examination. The two-way interaction term GD is the difference in effect of CGC vs OC between the subgroups, for example 1.09 - 0.62 = 0.47 for SPPB, age70-79 vs age 80+, 4 months.

Sletvold et al. BMC Geriatrics 2011, 11:18
http://www.biomedcentral.com/1471-2318/11/18

BMC Geriatrics

STUDY PROTOCOL Open Access

Effect of in-hospital comprehensive geriatric assessment (CGA) in older people with hip fracture. The protocol of the Trondheim Hip Fracture Trial

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Abstract

Background: Hip fractures in older people are associated with high morbidity, mortality, disability and reduction in quality of life. Traditionally people with hip fracture are cared for in orthopaedic departments without additional geriatric assessment. However, studies of postoperative rehabilitation indicate improved efficiency of multidisciplinary geriatric rehabilitation as compared to traditional care. This randomized controlled trial (RCT) aims to investigate whether an additional comprehensive geriatric assessment of hip fracture patients in a special orthogeriatric unit during the acute in-hospital phase may improve outcomes as compared to treatment as usual in an orthopaedic unit.

Methods/design: The intervention of interest, a comprehensive geriatric assessment is compared with traditional care in an orthopaedic ward. The study includes 401 home-dwelling older persons >70 years of age, previously able to walk 10 meters and now treated for hip fracture at St. Olav Hospital, Trondheim, Norway. The participants are enrolled and randomised during the stay in the Emergency Department. Primary outcome measure is mobility measured by the Short Physical Performance Battery (SPPB) at 4 months after surgery. Secondary outcomes measured at 1, 4 and 12 months postoperatively are place of residence, activities of daily living, balance and gait, falls and fear of falling, quality of life and depressive symptoms, as well as use of health care resources and survival.

Discussion: We believe that the design of the study, the randomisation procedure and outcome measurements will be of sufficient strength and quality to evaluate the impact of comprehensive geriatric assessment on mobility and other relevant outcomes in hip fracture patients.

Trials registration: ClinicalTrials.gov, NCT00667914

Background

Every year about 9000 persons undergo hip fracture surgery in Norway [1]. Hip fractures among older people are associated with high morbidity, mortality, disability and subsequent hospital and societal costs as well as reduction in quality of life [2-6]. A Study from Oslo, Norway showed that the proportion of patients living in nursing homes increased from 15% before to 30% after the hip fracture; the proportion walking without any aid decreased from 76 to 36%; and 43% of the patients lost their pre-fracture ability to mobilise outside their own home [7].

Older people with hip fracture often have extensive co-morbidity which is associated with functional impairments and frailty. The frailty phenotype is defined by deterioration of multiple organ systems including the neurological, musculoskeletal, cardiovascular, metabolic or immunological systems [8]. Frailty has been shown to be associated with falls resulting in injuries [9].

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Previous studies show improved outcomes when older people with hip fracture are cared for by a specialist multidisciplinary team [10-12]. Reports indicate improved efficiency of multidisciplinary geriatric rehabilitation especially regarding delirium, recurrent falls and fractures, and use of institutional care [13-15]. There is now a growing body of evidence supporting this approach [16,17] and recently evidence-based guidelines as for treating hip fracture patients have been developed,[18] although context and organisation of so-called hip-units differs widely [19].

However, the findings in these studies are not conclusive and we still do not know which specific input, if any, is crucial to beneficial effects. Is it the management of medical complications; is it a goal-oriented intervention by one single professional staff-member, i.e. the physiotherapist, nurse or physician; or is it related to a multi-component mix of some or all these?

In a previous study we have shown that treating acutely sick and frail older patients in a care pathway based on a geriatric evaluation and management service significantly reduced mortality and also improved patients' chances of living at home [20,21]. Therefore, it would seem reasonable that frail old hip fracture patients would benefit from comprehensive geriatric assessment (CGA) in the acute setting. Evaluation of efficiency of care pathways for hip fracture patients should emphasise both survival, general function; especially mobility and physical activity, but also quality of life (QoL) and caregiver burden, as well as costs. There is a strong focus in health care management today on the efficient use of limited resources, especially on shortening of length of stay (LOS) and lowering of costs. Furthermore, over the years LOS for patients with hip fracture has declined irrespective of settings and the organizing of health care, indicating that new models of care are less costly than traditional clinical pathways. However, shortening of LOS and reduced emphasis on acute and in-hospital rehabilitation may increase admission rates to nursing homes and reduce the quantity and quality of rehabilitation, and consequently reduce recovery of walking ability and function [22,23] and also shift costs between sectors.

In the present study we aim to investigate whether an alternative clinical pathway for hip fracture patients during the in-hospital acute phase applying CGA in an orthogeriatric ward may improve outcomes in the short (1 and 4 months postoperatively) and long (12 months postoperatively) term without introducing additional specific follow-up programs. Hopefully we will increase the knowledge of whether in-hospital treatment of hip fracture patients in a geriatric acute-unit primarily will improve mobility, and secondly increase the chance of being discharged to and live in their own homes, and improve function and self-rated health, while maintaining the new care pathway cost-neutral in comparison to treatment in a traditional orthopaedic unit.

In accordance with general guidelines for the development, evaluation and reporting of randomized controlled trials (RCT) for complex interventions [24] the purpose of the this paper is to present context and study design, a short description of intervention, outcome measures and power calculations and also procedures for the Trondheim Hip Fracture Trial. An extensive report on the intervention program will be published later.

Aims

Primary aim

- To estimate the effect on mobility 4 months after surgery of treating hip fracture patients in an orthogeriatric ward as compared to treatment in an orthopaedic ward.

Secondary aims

- To estimate the effect of the intervention on place of residence, gait, activities of daily living, mood and health related quality of life 1, 4 and 12 months postoperatively.
- To investigate change in gait control and daily physical activity through one year after surgery.
- To estimate the effect of the intervention on the use of health care resources and survival.
- To estimate the effect of the intervention on fear of falling and falls 4 and 12 months postoperatively.

Methods/design

Project context

The present study is conducted at St. Olav Hospital, the University Hospital of Trondheim, Mid-Norway. St. Olav Hospital also serves as a local hospital for 280.000 inhabitants of Soer-Troendelag County, admitting all hip fracture patients from this catchment area.

During the study period the Department of Orthopaedics will run a Trauma Unit consisting of 19 beds for inpatient orthopaedic care. While in the Emergency Department hip fracture patients are examined by the orthopaedic resident on call who in collaboration with the orthopaedic surgeon in charge establishes diagnoses and indication for surgery.

The Department of Geriatrics is organised as a formal unit of the Clinic of Internal Medicine consisting of a 10 bed-ward of acute geriatrics services linked to an out-patient facility. During a recent hospital reorganisation with cutting down of beds in the Department of Orthopaedics an orthogeriatric 5 bed-unit was established as an additional but still integrated part of the acute geriatric ward.

Being a new service for hip fracture patients routinely offered in parallel with the traditional orthopaedic care pathway, it was decided to evaluate potential benefits of this unit, now investigated through the present study. Enrolment of study patients was planned to start after a 4 months clinical run-in period for the new unit.

Study design

The study is designed as a RCT with parallel groups where the intervention of interest, a CGA and management of hip fracture patients taking place in this orthogeriatric unit is compared with traditional care in an orthopaedic ward.

Study population

All people over 70 years of age, with an acute hip fracture, previously being able to walk 10 meters, and living in their own homes or staying temporarily in an institution, suffering an intracapsular, trochanteric or subtrochanteric fracture, and able to give an informed consent, are invited.

Excluded are patients with pathological fractures or multi trauma injuries or with terminal illness not expected to live longer than 3 months or patients who have already been enrolled in this study. At study start the catchment area consisted of the City of Trondheim and the nearest municipalities. In case of slow recruitment we will use the option of expanding the catchment area to comprise all municipalities of Soer-Troendelag.

Intervention

Patients randomised to the intervention group are transferred directly from the Emergency Department to the orthogeriatric ward while control patients are transferred to the trauma unit at Department of Orthopaedic Surgery. Orthopaedic surgeons are responsible for the initial assessment, diagnosing of the fracture and decisions on type of surgery for both groups. Anaesthesiologists make preoperative assessments regarding analgesia, operability and perioperative anaesthesiological procedures. After surgery and for a limited time period all patients are observed in the recovery unit.

On request orthopaedic surgeons examine study patients in the orthogeriatric ward and supervise the staff. Geriatricians serve the orthopaedic ward equivalently.

The experimental intervention program is offered only during the acute hospital stay. The orthopaedic surgeons decide on traditional follow-up consultations after discharge irrespective of group allocation.

Experimental group

Physicians at the Department of Geriatrics or residents on call have the 24-hour medical responsibility pre- and postoperatively.

The treatment strategy is based upon CGA which is a systematic and multidimensional diagnostic process focusing on evaluation of frail elderly persons' medical, psychosocial and functional capabilities and limitations in order to develop a coordinated and integrated plan for treatment and long-term follow-up by the primary health care system [25]. An interdisciplinary team consisting of geriatricians and residents, nurses, physiotherapists and occupational therapists with special competence in geriatrics is responsible for the CGA program. The team emphasizes adequate nutrition, early mobilization and functioning in activities of daily living, initial in-hospital rehabilitation and early discharge planning. Discharge planning starts as early as possible involving all team members. Whenever possible, patients are recommended to receive post discharge rehabilitation in their own home. In addition to treatment of current medical conditions, the management program also focuses on factors related to the fall incident causing the fracture.

Control group

Control patients receive traditional treatment at the Trauma Unit and follow-up at the Orthopaedic Outpatient Clinic. All patients are referred for in-hospital physiotherapy. Staff nurses are responsible for the discharge planning.

Measures

Mobility as primary outcome is assessed using the composite measure of the Short Physical Performance Battery (SPPB) [26,27]. SPPB consists of three tasks: 10 second of standing balance in three different positions (side-by-side, semi-tandem and tandem); 4 meter timed walking at preferred speed; and time to rise from a chair five times [26]. Each task is scored on a 0-4 scale. A score of 0 is given if the participant is unable to complete the task. Scoring from 1-4 for each task is assigned based on quartiles of performance derived from the Established Populations for the Epidemiologic Study of the Elderly (EPESE) [27]. A summary score ranging from 0-12, with 12 as the best score is created by summation of scores from the three tasks. The test is suitable for scoring persons with a large range of functional levels. It has been shown to have acceptable internal consistency (Chronbach alpha = 0.76) and test-retest reliability [28], ability to predict functional decline, rehospitalisation and death in older patients after hospitalization [29] and also to measure change in mobility in hip fracture patients.

Mobility as secondary outcome is measured by the Timed Up & Go (TUG). According to the procedure time needed to rise from a chair, walk 3 meters, turn and walk back and sit down is measured [30]. The test is performed twice and the mean time (seconds) of the

two trials is used as outcome. In the original paper by Podsiadlo the second of two trials is used, while in an earlier intervention study we have described high reliability of using the mean of two [31]. For participants not able to complete two trials, only one trial is used. Participants are instructed to use walking aids support if used regularly. Repeated tests aim to obtain fast speed while preserving safety, irrespective of using walking aids or not. TUG is well validated [30] and has been used in several studies on hip-fracture patients to predict falls [32], to assess functional mobility [33-35] and to assess effect of home-based therapy [36]. A limitation of using TUG is that scoring presupposes that the person is able to perform all sub-components of the task. Mobility and mobilisation during the index stay will be measures by use of Cumulated Ambulation Score (CAS) [37].

Place of residence is used as a secondary outcome. Registrations of place of residence and change in place of residence are based on Gerica - the Electronic Health Record (EHR) of municipality of Trondheim by a procedure similar to one we have reported previously [20]. The typology differentiates between patients living in their own home, sheltered housing, nursing home, rehabilitation facility or hospital, respectively.

Activities of daily living (ADL) is measured using the Barthel Index [38] and Nottingham extended I-ADL scale [39] based on reports, if possible from the patient, from next of kin or from nursing staff. Supplementing Gerica ADL-scores are filled in by community nursing staff. The Barthel Index evaluates a patient's self-care abilities in 10 areas, including bowel and bladder control. The scoring depends on the person's need for help such as in feeding, bathing, dressing, and walking. The Barthel index was constructed for stroke patients but has also been extensively used in hip fracture patients. I-ADL scales measure a series of life functions necessary for maintaining a person's immediate environment-eg, obtaining food, cooking, laundering, house cleaning and phone use. The Nottingham extended I-ADL scale has been shown to be reliable and valid in patients undergoing surgery for osteoarthritis but may underestimate the sizes of the health gain, at least after arthoplasty [40].

Health Related Quality of Life

The EuroQol is a widely-used standardised measure of self reported health [41] using questions in five domains (EQ-5D) that is applicable to a wide range of health conditions and treatments providing a simple descriptive profile and a single index value for health. ***Pain*** is measured by a numeric rating scale (NRS) (0-10) [42]. The Charnley's Hip Score as used in the SAHFE protocol (Standardized Audit of Hip Fractures in Europe) is used as a supplement [43].

Gait

Gait assessments are recorded for a subset of participants being able to walk without assistance from another person and attending the 4- and/or 12-month evaluations at the outpatient clinic. These measurements are performed using an electronic gait mat GaitRite® which is regarded a reliable measure of spatio-temporal gait parameters also in elderly and frail people [44-46]. Participants should preferably walk the gait mat without walking aids. ***Physical activity*** is monitored in all patients when sensors are available for use. For these measurements we are using the small body worn accelerometer-based sensor ActivPal®[47], which is undergoing extensive evaluation in our research group [48].

Falls and fear of falling

Number of falls and fall related injuries are registered retrospectively in three ways at each follow-up; through medical records, and asking the patient and the next of kin. Fear of falling is assessed by a) asking a simple question: "Are you afraid of falling"-yes/no scored on a simple four-point Likert scale [49] and b) by applying the 7-item Falls Efficacy Scale International (FES-I) [50].

Cognitive function is measured by use of the Clinical Dementia Rating scale (CDR)[51] based on registrations from next of kin and the performance based screening tool of patients, the Mini Mental State Examinations (MMSE)[52].

Depression

To assess the effect of the intervention on depressive symptoms we use the Geriatric Depression Scale 15 (GDS-15) [53-55]. GDS-15 can be interpreted as an indication of presence/absence of depressive mood [56,57].

Health economics

We will compare direct costs related to treatment in the orthogeriatric ward vs orthopedic ward, readmissions, rehabilitation, care in institutions, and home care services by calculating the incremental cost effectiveness ratio (ICER) and use a non-parametric bootstrapping approach. We will assign a value to the EuroQol states using previously developed tariffs of values. Robustness of results to choice of value set will be discussed. Where there are incomplete (censored) benefits or cost data due to loss to follow-up we will use non-parametric methods to infer cumulative costs and benefits [58,59]. Information on time of death will be collected from the National Registry.

Hospital related information

Data on cause and duration of any hospital admissions during the trial period is extracted from participants' hospital records. Hospital records will also be the most important information source for medication, previous and present co-morbidity and data related to pre-, peri- and postoperative monitoring.

Consent and enrolment

Nurses on call in the Emergency Department will undertake eligibility screening of all hip fracture patients. If there is a free bed in the orthogeriatric unit patients fulfilling the inclusion criteria are informed about the study and asked to participate. Depending on general health, pain, anxiety and fatigue study information is given as a short version. Proxies are informed about the study when appropriate and/or available, especially in relation to patients whose consenting competence could be questioned. Written consent is collected primarily at admittance in the Emergency Department or occasionally on day 3 or 5 at the clinical ward where research assistants routinely give a second orally, and also a written version of the study information to be kept by the patient or proxy. Furthermore, participating patients consent to participation for all four data collection points, otherwise being excluded. Explicit oral consent is accepted for patients unable of writing. At each data collection point participants receive repeated information on the study.

Randomisation and allocation concealment

After giving their informed consent participants are enrolled and randomized to immediate transfer for medical treatment in the orthogeriatric unit followed by surgical treatment by orthopaedics and further geriatric work-up and management in the orthogeriatric unit, or to receive traditional care in the Department of Orthopaedics. Randomisation is performed by using a web-based computerised randomisation service at the Unit of Applied Clinical Research, NTNU. Randomisation is blocked, with a random block length being integrated into the programming.

Research assistants are monitoring all hip fracture patients admitted to the hospital. Occasionally eligible patients may mistakenly be transferred to the Orthopaedic Department without being evaluated for eligibility. If not already being transferred for immediate surgical treatment and within 24 hours since admittance, patients are informed about the study and asked to participate. If patients consent, they are enrolled and randomised according to the protocol. After surgical treatment these patients are transferred to the orthogeriatric unit or returning to the orthopaedic unit according to results of the randomisation.

Data collection

For practical reasons it is not possible to implement systematic blinding of testing during the hospital stay. For the 1-, 4-, and 12-month assessments testers will not have access to information about the patients' group assignment.

Background information on living conditions, physical and cognitive function before the fracture is collected for all participants starting already during the stay in the Emergency Department. On day 3 or 5 research assistants collect details from patients' on falls history, use of mobility aids, pre-fracture scoring of Barthel ADL-Index and Nottingham extended I-ADL Scale when the clinical condition makes it appropriate, or from proxies when they are available. These registrations will be used as explanatory variables in the statistical analyses.

Mobilisation is monitored using CAS during the 3 first days after the operation. On day 3 a research assistant attaches an ActivPal sensor anteriorly on the non-affected thigh for at least a 24-hour activity monitoring. The sensor is removed on day 5. On day 5 or the nearest working day a SPPB mobility score is completed by a research assistant.

Research assistants will continually scrutinise study forms on missing data. Missing data from proxies are collected through telephone calls, as is also information needed to fill in the CDR form. Electronic hospital records will give further information on clinical examinations, medication, blood tests and other investigations performed during the index stay.

The 1-month registration is performed by research assistants at the site where the patient is living, irrespective of location. This might be the patient's own home, a nursing facility or a rehabilitation institution. The time window is 4 weeks ± 5 days. For details on data collection and questionnaires, see Table 1. Information on Barthel ADL Index or Nottingham extended I-ADL Scale items are collected primarily from the patients depending of cognitive function, or alternatively from the proxy. Whenever possible, information on participants living at remote locations from St. Olav Hospital is collected by trained local physiotherapists hired as research assistants.

The 4-month registration is performed by a research assistant at the hospital out-patient facility applying the present infrastructure for testing aspects of mobility and gait using the electronic gait mat. To secure maximal study compliance and low attrition rate, transportation both to and fro is taken care of by the same experienced taxi driver. An ActivPal sensor is worn for at least a 96-hour period of activity monitoring. Participants are urged to be tested at the hospital. In case of extensively impaired physical or mental capacity a pragmatic and reduced test protocol is applied in their own home or where they are staying for the time being. The time window is 4 months ± 2 weeks. For details on data collection and questionnaires, see Table 1.

The 12-month registration is performed similar to the 4-month registration. The time window is 12 months ± 4 weeks. For details on data collection and questionnaires, see Table 1.

Table 1 Measures, scales, questionnaires and time-points of data collection

Index stay	1 month postoperatively	4 and 12 months postoperatively
CAS (3 days)		
SPPB	SPPB	SPPB
TUG	TUG	TUG
	Place of residence	Place of residence
	MMSE	MMSE
	GDS-15	GDS-15
	FES-I	FES-I
	EQ-5D	EQ-5D
	NRS-pain	NRS-pain
ActivPal (24 hours)		ActivPal (4 days)
		GaitRite
Hand grip strength	Hand grip strength	Hand grip strength
		Quadriceps strength
Before fracture:		
Barthel Index	Barthel Index	Barthel Index
NEIADL	NEIADL	NEIADL
Falls	Falls	Falls
Walking aids	Walking aids	Walking aids
CDR	CDR	CDR

Abbreviations: CAS = Cumulative Ambulation score, CDR = Clinical Dementia Rating, EQ-5D = EuroQual-5 Domains, FES-I = Falls Efficacy Scale-International, GDS-15 = Geriatric Depression Scale, MMSE = Mini Mental State Examination, NEIADL = Nottingham extended Instrumental Activities of Daily Living, NRS = Numeric Rating Scale, SPPB = Short Physical Performance Battery, TUG = Timed Up & Go.

Adverse event management

Mortality rate is closely monitored. If the mortality rate becomes 50% higher for the intervention group the trial steering committee will be asked to evaluate individual case notes, reports and general aspects. The trial will be closed if the difference holds a significance level $p < 0.10$.

Power and statistical analyses

Sample size estimates are based on mobility assessed by SPPB at 4 months following the fracture. A change in the SPPB score of 0.5 points is considered a small but meaningful change, while 1 point is considered a more substantial change. In order to detect an effect size of 1.0 when power is 80% and alpha = 0.05, a sample size of 304 participants would be needed. Based on data from a previous prospective observational study in a similar study population (work in progress), we expect a drop out rate of 10% due to death and 10% due to withdrawals during the first 4 months following the fracture. To allow for 304 patients to remain in the project at four months after the fracture 380 persons need to be included. Thus, the plan is to include a total sample of 400 participants. The assumptions underlying the sample size (i.e. the standard deviation at baseline) has been checked by an independent clinical trials unit after the first 200 patients enrolled, and found to be acceptable.

All data will be analysed and presented according to the updated CONSORT guidelines for reporting parallel group trials[60]. Patterns of missing data will be explored prior to analysis, and accounted for in the analysis by imputation methods [61]. To study differences in change between groups we will use multivariate analyses by use of mixed models for longitudinal data by general linear modelling (GLM) for continuous outcomes and by logistic regression for binary outcomes [62]. To study associations between the new clinical pathway and time to events, we will use Kaplan Meyer plots and the Cox proportional hazards regression model. In all analyses we will control for confounding factors and interactions and present both unadjusted and adjusted effects with 95% confidence intervals.

Time plan of the study

Since study start on April 18th 2008 until December 30th 2010 altogether 1077 hip fracture patients have been admitted to the Emergency Department at St. Olav Hospital, Trondheim University Hospital and screened for eligibility, of whom 401 have consented to participation, see Figure 1.

The final 12-month registrations will take place in December 2011. The formal analyses are estimated to start when the data base on the 4-month primary endpoint measures of mobility is finalised by May 2011. With exception of the study statistician, the study team will be masked from the trial results until the final follow up is completed.

Ethics and approvals

The study is approved by the Regional Committee of Ethics in Medical Research (Mid-Norway) (REK4.2008.335), the Norwegian Social Science Data Services (NSD19109), and the Norwegian Directorate of Health (08/5814).

Discussion

Presenting this paper of the study protocol covering design, outcome measures, power calculations and procedures of the Trondheim Hip Fracture Trial is in accordance with general guidelines for reporting of RCT protocols for complex interventions [24], although it is published after the conclusion of the recruitment phase but still before the onset of data analysis and while the data collection is going on.

The objective of the study is to evaluate the impact of CGA on older hip fracture patients still having potential of functional improvement and preservation of health related quality of life aiming at prolonging their ability

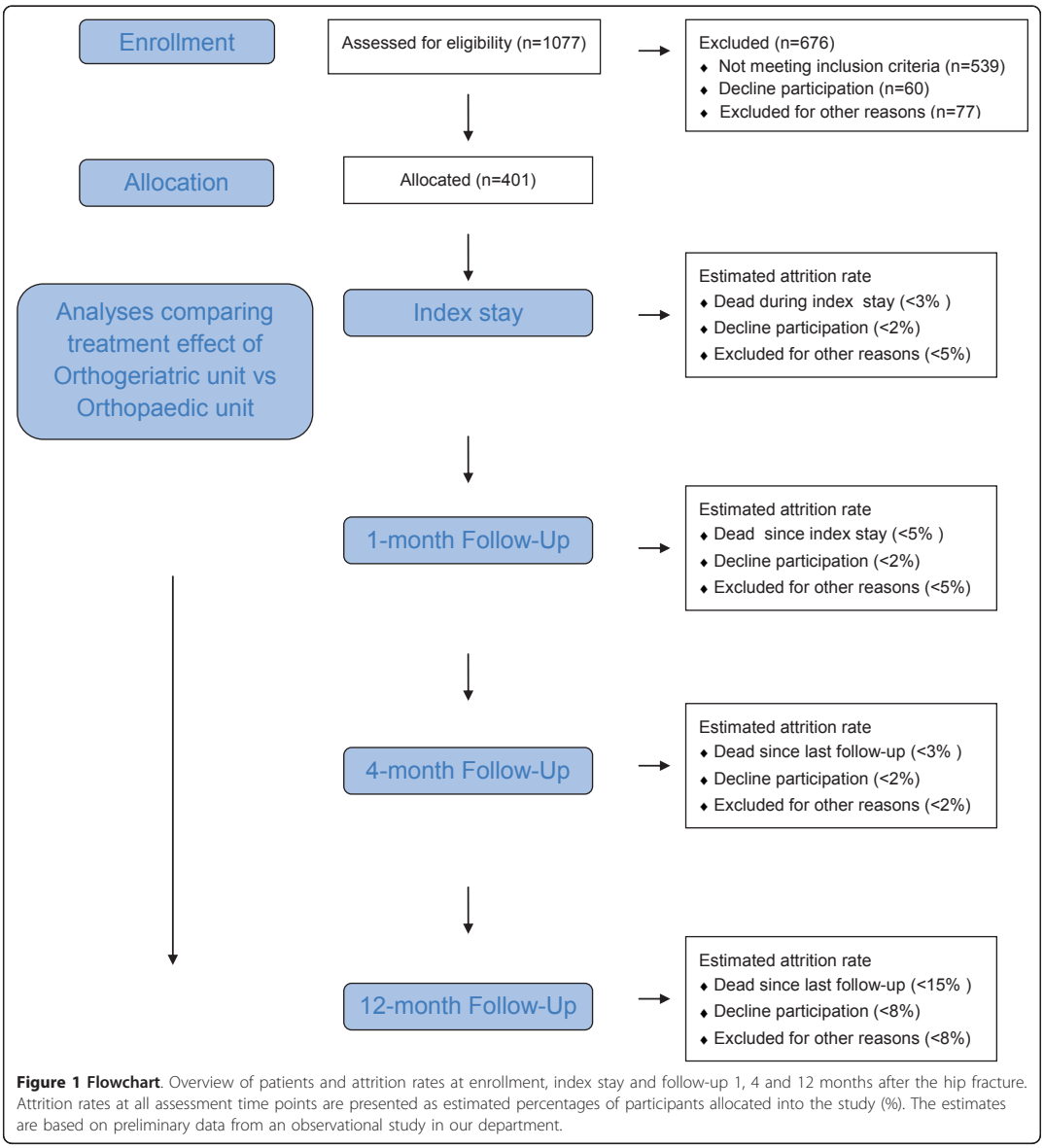

Figure 1 Flowchart. Overview of patients and attrition rates at enrollment, index stay and follow-up 1, 4 and 12 months after the hip fracture. Attrition rates at all assessment time points are presented as estimated percentages of participants allocated into the study (%). The estimates are based on preliminary data from an observational study in our department.

to live in their own home. Excluded are young hip fracture patients, patients with terminal illness, permanent nursing home residents and patients unable to walk. Patients with cognitive impairment and also temporary nursing home residents are included, representing patients known to be at especially high risk of further deterioration. Therefore, the study sample should comprise the most relevant segments of hip fracture patients regarding measurable benefits of CGA, being neither too healthy nor too ill.

We have chosen mobility as the primary endpoint, mainly because impaired mobility is one of the most feared consequences of a hip fracture in addition to death and nursing home placement, hopefully being accessible for intervention [16]. Still, potential benefits of CGA on mobility at 4 months will be more or less an

indirect consequence of the intervention. Although mobility has been defined as the most important outcome, several secondary study outcomes i.e. ADL and I-ADL, health related quality of life, the extent of being discharged to own home, and costs may be equally relevant. This study is not sampled for mortality and nursing home placement as endpoint, and thus this information will only be used for hypothesis generation for future studies.

The context and organisation of care pathways for hip fracture patients differ extensively even in a small country like Norway. Nevertheless, there are consistent efforts by hospital managements towards shortening of hospital LOS based on fast-track orthopaedic services. Important consequences are less time for stabilisation of clinical conditions, assessment and treatment of relevant co-morbidity, as well as shifting of rehabilitation services out of hospitals, contrasting important constitutive elements of CGA-based specialist services.

Since the present intervention program will not implement any kind of medically follow-up by geriatric specialist services, and recommendations are to be dealt with by general practitioners and nursing homes or rehabilitation facilities outside hospital, important aspects of CGA may be lost. However, the competence and compliance of primary health care system vary extensively. Limitations of the study might thus be related both to study sample, non-blinding of assessors and choice of endpoints, as well as content and performance of the experimental intervention program.

The most important challenge is still the black box of inter-linked elements of CGA, of which we still do not know what is actually working. Therefore, evaluating the benefit of CGA within the present context without including an extended and optimal geriatric rehabilitation service or a relevant follow-up program after discharge from hospital may in fact increase the knowledge base as to the most important elements of CGA. The present study will hopefully be able to designate potential predictors of a successful or non-successful care pathway.

To our knowledge the present study is the largest and most comprehensive RCT investigating CGA on elderly persons having suffered a hip fracture. There is however need of more research on alternative care pathways [16]. As a second step our research group is now implementing two studies. The first one will focus on potential benefits of a more extensive involvement of and follow-up by the community care system including physiotherapy in the patient's own home to start immediately after discharge from hospital or after returning home from an out-of-hospital rehabilitation facility. This is a case-control study with historic controls from the present study. The second study is a RCT investigating the potential effect of a boost of a 10 weeks intensive physiotherapy program 4 months after the hip fracture.

In conclusion we believe that study design, randomisation procedure and outcome measurements will be of sufficient strength and quality to evaluate important impacts of CGA during the index stay on mobility and other relevant outcomes in hip fracture patients.

Acknowledgements

The study was initially funded by the Norwegian Research Council (NFR grant 186515), and later supplied by grants from the Central Norway Health Authority and the Department of Neuroscience, NTNU, the St. Olav Hospital Trust, the SINTEF and St. Olav Hospital Fund for Research and Innovation, and the Municipality of Trondheim.

The staff of the Department of Geriatrics and the Trauma Unit, Department of Orthopaedic Surgery and also the Emergency Department are highly acknowledged for more than 2 1/2 year of extensive participation in a comprehensive and challenging trial both regarding work-load, logistics and professional attitude. Vigleik Jessen and Eiliv Brenna, heads of the clinics of Orthopaedics and Rheumatology and Internal Medicine, respectively, are especially acknowledged for decisive support at initiation and establishment of the orthogeriatric service, and also during troublesome funding processes. The Unit of Applied Clinical Research, NTNU is acknowledged for excellent web-based computerised randomisation service.

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Authors' contributions

OS initiated the study, has led the work on research design, intervention and implementation of the study protocol and is the primary author of the manuscript. JLH and IS have made substantial contributions to the conception of the study, research design, intervention and implementation of the protocol. PT and KT have made substantial contributions to the implementation of the study protocol, testing and ongoing data collection. SL made important contributions to the research design and conduct of the study. AP has participated in the implementation of the study protocol and is extensively involved in the ongoing data collection. AA, RJ and JM made important contributions to the study protocol. All authors contributed to the writing and review of the manuscript and approved the final version.

Competing interests

The authors declare that they have no competing interests.

Received: 6 February 2011 Accepted: 21 April 2011
Published: 21 April 2011

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Pre-publication history
The pre-publication history for this paper can be accessed here:
http://www.biomedcentral.com/1471-2318/11/18/prepub

doi:10.1186/1471-2318-11-18
Cite this article as: Sletvold *et al.*: Effect of in-hospital comprehensive geriatric assessment (CGA) in older people with hip fracture. The protocol of the Trondheim Hip Fracture Trial. *BMC Geriatrics* 2011 **11**:18.

The Trondheim Hip Fracture Trial

"A new clinical pathway for patients with hip-fracture"

Clinical trial analysis plan

Content:

1. Background

1.1 Aims of the study

The aim of this RCT is to investigate effectiveness of treating elderly patients with a hip fracture in a specialized orthogeriatric unit, as compared to standard care in a traditional orthopedic unit.

Primary end point is mobility after 4 months as evaluated by the Short Physical Performance Battery (SPPB). Secondary end points are specified physical, emotional and cognitive functions, and place of residence at 1, 4 and 12 months and costs of the new versus the old treatment.

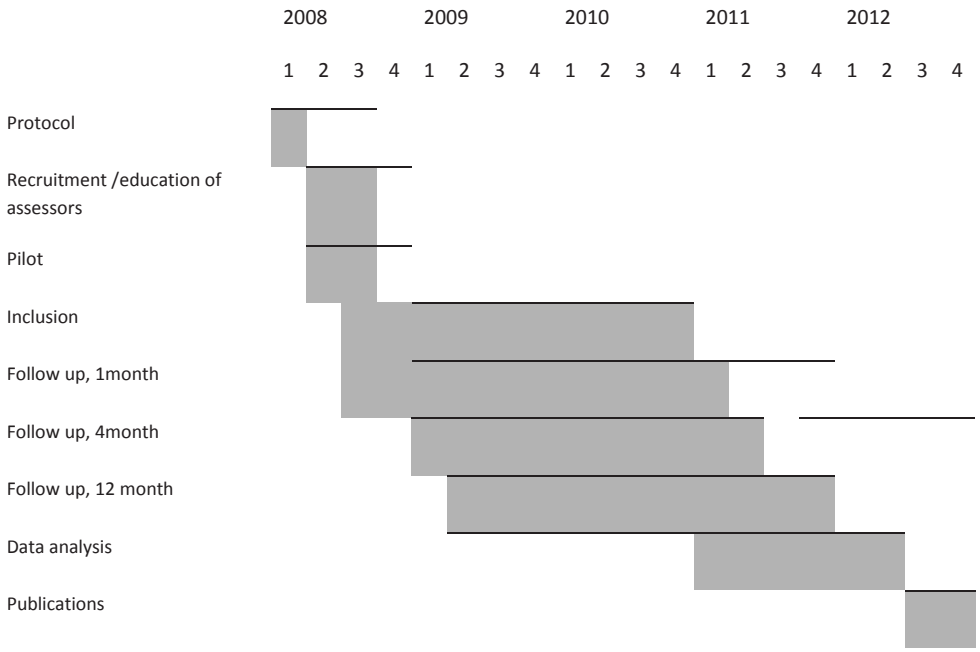
1.2 Eligibility criteria

All patients diagnosed at St Olav's University Hospital with a proximal femur fracture (ICD 10 code S72.0, .1 and .2) from mid April 2008 until finishing recruitment on December 30th 2010 were eligible for inclusion.

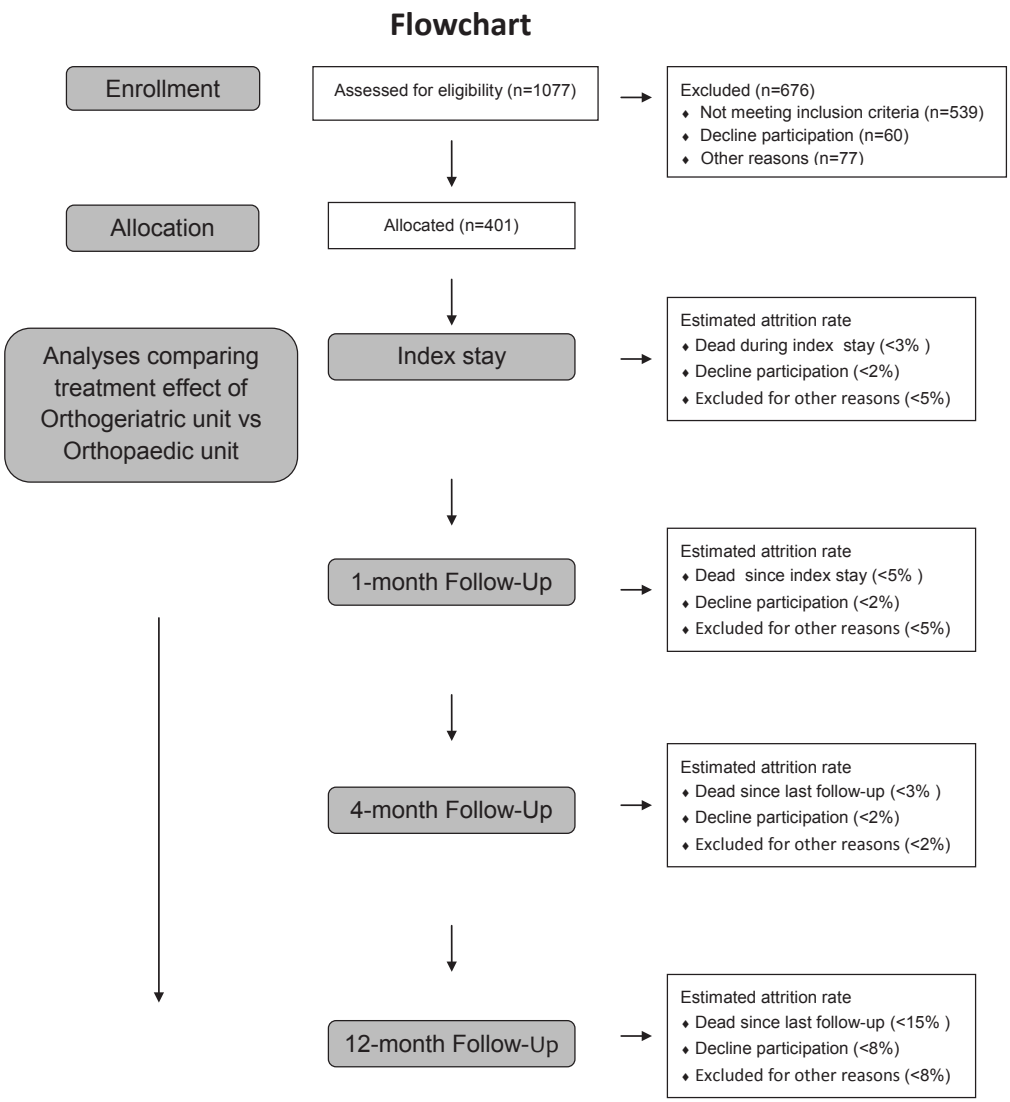
Inclusion criteria	Exclusion criteria
Age > 70	Pathological fracture or multi-trauma
Registered home address in Sør-Trøndelag	Terminal illness, not expected to live longer than 3 month
Hip-fracture, including collum fractures, trochanteric fractures and sub-trochanteric fractures.	Already included in the study because of a recent hip-fracture
Able to walk 10 m without assistance from a person before the fracture	
Living at home or temporar stay in an institution	

Participation is voluntarily and according to the Helsinki declaration. The patient or next of kin give a written informed consent before enrollment.

1.3 Timeline:


2008
2009
2010
2011
2012
1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4
Protocol
Recruitment /education of assessors
Pilot
Inclusion
Follow up, 1month
Follow up, 4month
Follow up, 12 month
Data analysis
Publications

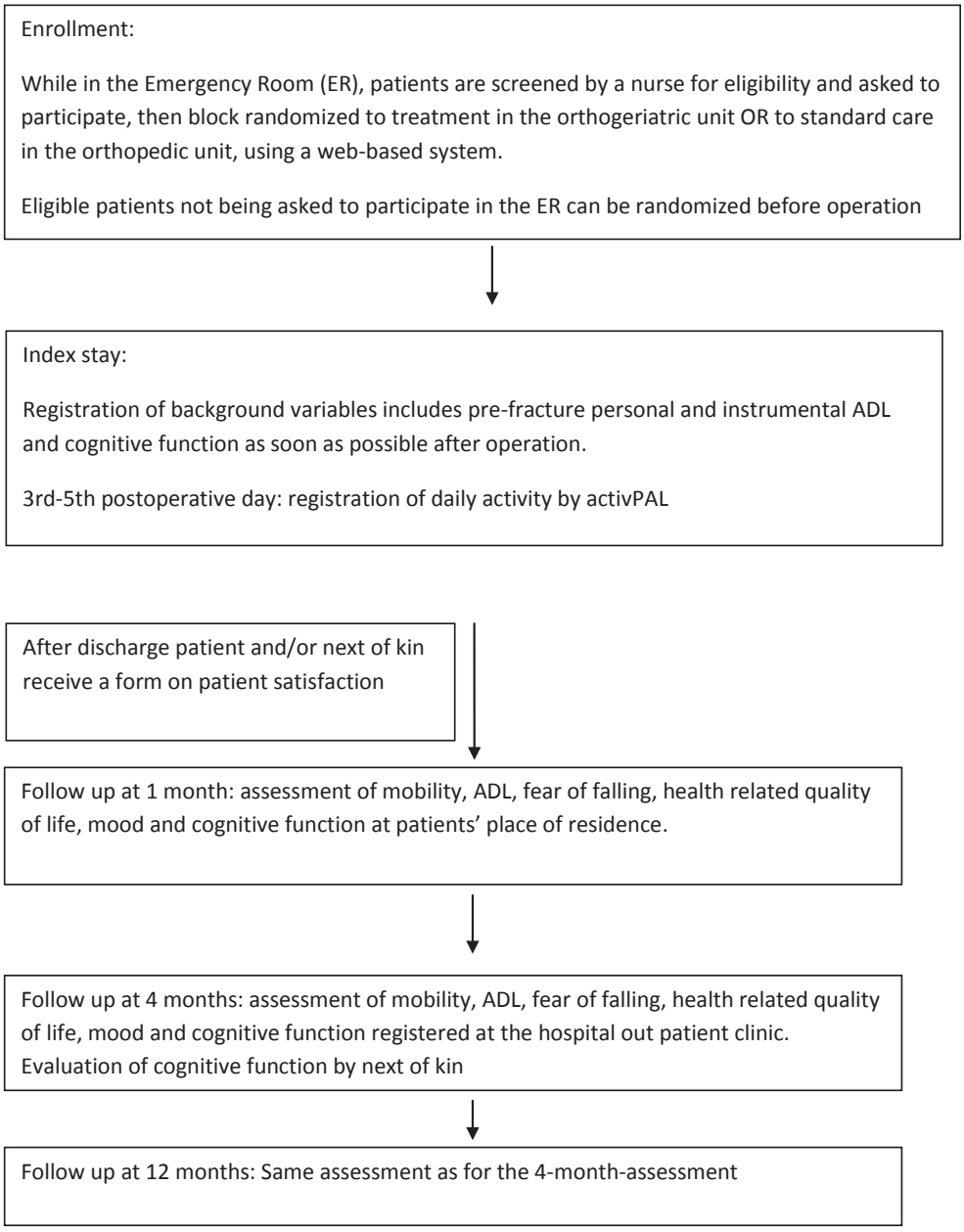
1.4 CONSORT flowchart



1.5 Design

The study is a block randomized controlled study.

Assessment schedule:



1.6 Power and statistical analyses

Sample size estimates are based on mobility assessed by SPPB at 4 months following the fracture. A change in the SPPB score of 0.5 points is considered a small but meaningful change, while 1 point is considered a more substantial change[1]. In order to detect an effect size of 1.0 when power is 80% and alpha = 0.05, a sample size of 304 participants would be needed. Based on data from a previous prospective observational study in a similar study population (work in progress), we expect a drop out rate of 10% due to death and 10% due to withdrawals during the first 4 months following the fracture.

To allow for 304 patients to remain in the project at four months after the fracture 380 persons need to be included. Thus, the plan is to include a total sample of 400 participants. The assumptions underlying the sample size estimation (i.e. the standard deviation at baseline) has been checked by an independent clinical trials unit after the first 200 patients enrolled, and found to be acceptable.

1.7 Harm

We have performed an interim analysis on early mortality including the first 200 patients. Our predefined end point was 50% excess mortality in the intervention group with a P-value of 0.1. Mortality was not increased in the intervention group and the study inclusion therefore continued as planned.

2. Populations

2.1Total study population

A total of 1077 patients entering St Olav's Hospital with a proximal femur fracture from April 17th 2008 to December 30th 2010 have been registered. The inclusion period was terminated when 401 patients fulfilling the inclusion criteria had been correctly randomized.

2.2 Intention to treat population

Of the 436 patients being randomized 35 did not meet the inclusion criteria (error during inclusion). The 401 fulfilling the inclusion criteria and being correctly randomized will be included in the intention to treat analyses regardless of actual received treatment. Patients not fulfilling the inclusion criteria but still being randomized by mistake will be described with respect to diagnose, gender and age and group allocation.

2.3 Efficacy/treated population

Efficacy analyzes will be performed on patients who have been randomized correctly and having received the intended interventions. Two cases did not receive allocated treatment (one in each group). Patient data exclusive protocol violators will be analyzed separately after initial analysis according to intention to treat.

2.4 Pre planned sub group analysis

Prespesified subgroup analysis will be performed on the following subgroups:

-Old versus new orthopedic ward: During the study period the orthopedic ward moved from an old to a new building. We will evaluate whether change in the physical environment have an impact of the results in the study for primary end point of SPPB, place of residence and patient/proxy satisfaction.

- Subgroups of frailty: Subgroups identified by combining Barthel, Nottingham and CDR scores and frailty measures will evaluated as for potential differing effects on the SPPB and place of residence and fear of falling at 1, 4 and 12 months. We will also perform a separate cost utility analysis for the frail patient group.

3. Datasets

3.1 Registered datasets

Data being collected during the index stay (including data of premorbid function) and at 1, 4 and 12 months after the fracture and information from questionnaires being sent to patient/next of kin after discharge.

3.2 Imputation of data

Patterns of missing data will be described and analyzed, and appropriate methods of imputation will be chosen accordingly for separate groups of missing data based on the chosen statistic that will be used to assess group differences of change [2]. We will examine the baseline characteristics of those participants with missing data, by randomization group to determine whether there are systematic differences between groups.

We will use imputation on missing data due to 3 mechanisms:

i) Missing at random- eg not participating at a single control due to i.e. bad weather.

ii) Missing completely at random- eg: data missing due to loss of single forms during follow up.

iii) Not missing at random- eg: patients who refuse to perform a test because of pain.

No separate imputation will be performed if analyzing with mixed models (auto imputation is part of model).

4. Protocol violators

4.1 Ineligible patients

Thirty five patients were enrolled by mistake without fulfilling the inclusion criteria. For these patients only data on diagnoses, gender and age are registered. These patients will not be included in the intention to treat neither the efficacy analyzes.

Reasons/mistakes:

-Age below 70 years

-Not suffering fracture

-Permanent resident in nursing home

-Not able to walk before fracture

-Misunderstandings on refusing of participation

We will report group belonging for violators and if they are unevenly distributed between groups.

4.2 Non –adherence

Patients withdrawing from the study before discharge from the index stay and patients treated in wrong department according to randomization will be included in the intention to treat analyses and analyzed according to the randomization result.

4.3 Withdrawals

All withdrawals and reasons for withdrawals from the study will be described for each treatment arm:

i) Withdrawal from

ii) Withdrawal from follow up. Some patients refuse to participate at scheduled assessments, but have accepted data from journal and registries to be used.

iii) Withdrawal of consent. Data up till time of withdrawal will be included in the analyses.

4.4 Missing follow up

Some patients have not met for single scheduled assessments or have no data on single tests in scheduled assessment. These will be included in the intention to treat analysis.

A complete list of violators and ineligible patients will be made up before any analyses of data are performed.

5. Derived variables

Most variables are scored by assessor except patient satisfaction which is scored by patient/next of kin. Gaitrite and ActivPal are registered electronically. Forms are then scanned and checked by assessor or are plotted manually (SPPB, TUG and CDR).

Assessment and measurements

5.1 Gait/balance /strength

i) SPPB- Short physical Performance battery

We will use the test as described by Guralnik [3]with a total score 0-12 points in 3 different modalities- standing balance, 8 foot walk and sit to stand from a chair- and a maximum score of 4 points in each modality with the highest score for the best performance. 1 points difference in total score is found to be substantial , while 0.5 points is found to have a small but meaningful effect[4].

ii) TUG –Timed up and go

Time is measured as the patient raises from chair, walks 3 meters, turns and walk back before she sits down[5]. In a old home dwelling population 16 seconds [6] is a cut-off that signals risk of falling, while 24 seconds is found to be a cut-off after a recent hip fracture[7].

iii) Gaitrite

Patients walk over an electronic carpet while their pattern of walking is registered [8].

A separate protocol will be developed for analysis of these data.

iv) ActivPal

Measurement of in –hospital activity by a small body worn accelerometer-based sensor ActivPal® [9] is found to be a good measurement of daily activity, and the method is evaluated by our group for our patient group [10]. A separate protocol will be developed for analysis of these data.

v) Muscle strength

Grip strength measured with a dynamometer is shown to be fairly representative for total body strength and health condition. Low grip strength is associated with increased risk of low mineral bone density [11], falling and suffering a hip fracture [12]. We have also measured bilateral isometric quadriceps strength at 4 and 12 months with a digital dynamometer, where force is measured as Nm.

5.2 ADL

i) Barthel Index

The Barthel Index is used to evaluate activities of daily living [13]. This scale has been used in a large number of studies, and is established and validated in hip fracture patients.

5.3 Instrumental ADL

i) Nottingham Extended IADL scale

The Nottingham scale of I-ADL is a tool that is well established and validated in hip fracture patients. It was primary designed as a tool for measuring iADL function for patients suffering from stroke[14], but is later also used in hip fracture patients[15] and patients with hip replacement[16].

5.4 Cognitive function/psychiatric symptoms

i) CDR

We have used a Norwegian version of the CDR scale by Hughes[17] which is a 6 items scale with scores of 0 to 3 points on each item. It can be used in two ways:

i) Memory is primary item; the other items (orientation, judgment/problem solving, community, home/hobbies and personal care) are secondary items. The memory score gives the score of the test. If three or more secondary scores are 1 point higher or lower than the primary score, the result is adjusted according to the difference.

ii) It can also be used as a continuous scale with an average score on all items as main score, as shown by Engedal.

ii) MMSE

The Mini-Mental Status Examination MMSE) is well established as a screening tool for cognitive impairment in older persons [18]. MMSE is not measured during the index stay.

iii) Geriatric Depression Scale

GDS-15 is a well established tool to assess depressive symptoms in older people. It consists of a 15 items questionnaire where 0-5 is normal, 5-9 indicating mild and >10 moderate to severe depression. The GDS-15 score is shown to affect results of rehabilitation in hip fracture patients[19].

5.5 Quality of Life

i) EuroQol

EuroQol [20] is established to evaluate quality of life. Each participant scores his mobility, ability of self-care, activities, pain/discomfort, and anxiety/depression. The result is presented as a 5-digit number. In addition we use the EuroQol thermometer were each patient grades his quality of life on a 0-100 point scale.

5.6 Patient/proxy satisfaction

i) PasOp

Patient/proxy satisfaction with in-hospital stay is measured with the PasOp which is sent to patient/next of kin at discharge after the index stay. This questionnaire is used by the Central Norway Regional Health Authority and produced by Heltef (Foundation for Health Services Research). The questionnaire consists of 36 items regarding experiences and 8 items regarding courtesy and respect by the staff. In addition it contains a 9 item form asking for suggestions regarding needs of improvement of staff (nurses, physicians), organization, equipment, treatment of next of kin, information (drugs, investigations, discharge procedures) and communication.

The questionnaire is validated by regular use in the region, but not for older hip fracture patients per se.

Data have not been collected from proxy if the patient died during the index stay.

5.7 Health economy

i) EuroQol

See 5.5. We will use qualys [21] as a part of our economic analysis to create a generic picture of cost of the interventions.

ii) Use of recourses

We have decided to use a cost utility approach[22] with measurement of direct costs of health services related to outcomes. As the primary outcome is difference in SPPB at 4 months, this will be the primary outcome in the analysis, but other significant differences between groups on secondary end points will also be subject of cost analysis.

We have not registered indirect costs or costs outside the public health service due to difficulties with reliable registration of data. If there are indications of differences between groups i.e. a major difference regarding people living at home at 4 and 12 months after the hip fracture, an estimation of indirect costs based on registrations by Statistics Norway will be considered.

Direct costs consist of:

i) In-hospital use of resources during the index stay-

- Length of stay including total length of stay and time from admission to registration of “ready for discharge”.

- Costs per day .We will use a calculated average costs for each group per day and not the actual costs. Due to differences in DRG coding in the orthopedic ward versus the geriatric ward we will use a registration of total cost regardless of funding based on DRG.

ii) During a 12 months follow-up use of in-hospital resources post discharge, including visits at specialist out patient clinics.

iii) Use of resources in the primary health care system

- Time in rehabilitation facilities. We will calculate an individual average cost differentiating between types/level of rehabilitation.

- Home care including nursing and home help by the municipality authorities.

-Use of physical or occupational therapy.

-Use of primary health care physicians (GPs)

A table specifying cost categories, units, source of data, unit prices in Euro, see Addendum.

5.8 Fear of falling

i) FES-I, short form

The original FES-I is a validated scale measuring fear of falling and the social consequences of fear of falling [23]. The newly developed short form is found to have a good correlation and similar abilities as the original FES-I [24]. A Norwegian version has recently been validated[25].

ii) 4 point Likert scale of fear of falling

The scoring 0 indicates not worried, 1- slightly worried, 2- rather worried, 3- very worried. This is also a part of Standardized Audit of Hip Fractures in Europe (SAHFE) protocol (5.9)

5.9 SAHFE interview

i) Pain

a) NRS 11

We use the NRS 11 scale for evaluation of pain. This scale is widely used for evaluation in clinical settings and has a good face value. We have not used it as a ratio scale, as recommended in literature[26].

b) Charnley hip score

The Charnley hip score is a grading of pain from no pain to the worst thinkable pain and is established and recommended by the Standardized Audit of Hip Fractures in Europe (SAHFE) [27].

c) SAHFE questions on pain

Questionnaire with 6 items grading pain in operated foot from no pain, occasional light pain, pain in activity, moderate pain with limitation of activity, strong pain not allowing activity and strong pain even with no activity.

ii) SAHFE questionnaire mobility

Indoor and outdoor use of aid , 6 items from no aid, one cane/crutch, 2 canes/crutches, walker, wheelchair, able to walk with support and wheelchair not able to walk.

Change in walking ability after fracture, 3 alternatives- no change, some negative change due to fracture, some negative change independent of fracture.

iii) Registration of falls:

A simple registration of number of falls, having 3 alternatives: no falls, 2 or less falls, more than two falls. Space for free text describing fall.

iv) Fear of falling

See 5.8

5.10 Background variables

i) Charlson score

This is a co-morbidity score performed by evaluation of patient medical history and subsequent risk of complications based on a limited number of diseases[28]. The patient is scored from 1 to 6 points if he suffers from a disease on the Charlson list. The score is cumulative. We will use the ICD-10 adapted scoring system.[29]

5.11 Clinical variables

i) APACHE II

APACHE (Acute Physiology And Chronic Health Evaluation) is a scoring system for grading risk of morbidity and mortality for acute sick patient[30]. It consists of a mix of different variables including acute physiological parameters (pulse, blood pressure, temperature and respiratory status), Glasgow Coma Scale, lab values (oxygen saturation, hematocrite, leukocytes, sodium, potassium and creatinine) and evidence of chronic disease (heart-, kidney-, respiratory-, and liver failure) and failure of the immune-system. We have used the APACHE II version[31].

The APACHE scoring system is generally used in studies of intensive care settings, but is also used as a grading system of preoperative risk, and is also used to evaluate the risk of geriatric patients with a hip fracture[32].

5.12 Baseline and clinical variables

i) Social status

a) Residence- regular or sheltered housing

b) Home care- general aid and/or in home medical care

c) Living alone- unmarried, married, divorced, widowed

d) Children

e) Use of walking aids

ii) Medical history at baseline

a) Contact with hospital 12 months before fracture

b) Fractures 10 years before hip fracture

c) Known osteoporosis

d) Charlson score

iii) Fracture type

a) Femoral neck fracture, and using the Garden classification dichotomized in non-dislocated (Garden 1 and 2) or dislocated (Garden 3 and 4)

b) Pertrochanteric fracture

c) Subtrochanteric fracture

iv) Pre-operative data

a) Door to needle time specified as registered time of entry into hospital to start of preparation for surgery in the theater.

b) Preoperative evaluation including ASA score and the need of medical evaluation other than surgeon and anesthesiologist (cardiologist or other)

v) Periperative data

a) Blood loss

b) Periperative pulse and blood pressure measurements

c) Operating time defined as time with surgeon working on patient.

vi) Postoperative data

a) Fracture related complications - infections (superficial or deep), dislocation of hip, reoperation

b) General complications- death, renal failure, stroke, heart attack, pulmonary embolism

vii) Mobilization

Cumulated ambulation score (CAS) is a measurement of the degree of active mobilization during the index stay and is measured at day 3 to 5 during the postoperatively [33] .

viii) Medication

a) Medication at admission

b) Medication at discharge

6 Outcome variables

6.1 Clinical effectiveness

In line with the aims of the study our outcome variables are as follows:

i) Primary outcome

1) Mobility

SPPB measured as described at 4 months.

ii) Secondary outcomes

See Table 2 for time of assessment of secondary outcomes.

Table 2

OUTCOMES	Prefracturefunction	Index stay	Follow up 1month	Follow up 4 month	Follow up 12 month	patient	proxy	Med. -
p-ADL	Barthel index		Barthel index	Barthel index	Barthel index	X	X	
I-ADL	Nottingham ext		Nottingham ext.	Nottingham ext.	Nottingham ext	X	X	
	New mobility score		New mobility sore	New mobility score	New mobility score	X	X	
	IPLOS		IPLOS	IPLOS	IPLOS			X
Gait/balance			TUG	TUG	TUG	X		
			SPPB	SPPB	SPPB	X		
				Gaitrite	Gaitrite	X		
				Biodex	Biodex	X		

Cognitive function	CDR		MMS	MMS CDR	MMS CDR	X	X	
Health related quality of life	EQ-5D		EQ-5D	EQ-5D	EQ-5D	X		
Depression	GDS 15		GDS 15	GDS 15	GDS 15	X		
Fear of falling	FES-I		FES-I	FES-I	FES-I	X		
Fall	SAHFE		SAHFE	SAHFE	SAHFE			X
Activity level		Active pal		(Active pal)		X		
Medical registrations		Test results complications treatment	Test results complications treatment	Test results complications treatment	Test results complications treatment			X
Health economy	Place of residence, home care services, institution last 14 days		Place of residence, home care services, institution/ hospitalization EQ-5D	Place of residence, home care services, institution/ hospitalization EQ-5D	Place of residence, home care services, institution/ hospitalization EQ-5D			X
Patient/proxy experience		PasOpp		Interviews of selected populations		X	X	

7. Data quality control

During scanning of data we have performed a continuous control of input: random samples of scanned forms (10% total) are controlled afterwards to check for errors.

Comments/supplementary information on forms are registered in a separate computer based log.

Plotting of data is performed by 2 persons working together. Control of plotted data includes check of 10% of the data.

Complete data files are checked for errors by descriptive statistics, performing extra checks on outliers.

8. Statistical analysis

The data will be summarized and analyzed according to the aims of the trial and as described in Sletvold et al BMC Geriatrics 2011 and registered in ClinicalTrials.gov.

The analysis will be performed by PASW (SPSS) version 17 or 18 from IBM and STATA by Stata Corp.

We will use 2-sided tests with a significance level of 5%. The results will be presented as means and 95% confidence interval for continuous data, median and interquartile range for ordinal data and numbers and percentage for dichotomous data.

To study differences between groups for mobility outcomes at four months we will use multivariate analyses by use of ANCOVA, controlling for variables possibly influencing the results [34]. Outcomes at four months with available baseline values will be assessed by general linear modeling (GLM) for continuous variables and by logistic regression for binary variables.

Change in outcomes from one to four to twelve months will be assessed by longitudinal ANCOVAs or by GLM. When analyzing data related to place of residence we will use survival analysis with Cox proportional hazard

Mixed model analyses will be considered according to pattern and extent of missing data.

8.1 Recruitment

The numbers and percentage of participants left in the study at the different stages will be published as shown in the CONSORT diagram in section 1.4[35].

We will analyze withdrawals and protocol violators related to randomization group.

8.2 Demography/baseline

Data will be presented as mean, median, standard deviation, interquartil range or n and percentages..

i) Demography

a) Age, gender and place of residence will be reported

a) All patients screened in the study will be reported (total population)

b) All patients randomized including those randomized by error will be reported

c) Eligible patients randomized and included (ITT) will be reported

ii) Baseline data

Background variables including clinical data during index stay are listed in section 7.1. will be reported for randomized patients. Data are not reported for ineligible patients randomized by mistake.

8.3 Clinical effectiveness

Analysis will be performed according to

i) Intention to treat. There are no data on ineligible patients. Primary analysis will be on observed datasets, secondary on data including imputed variables.

ii) Efficacy assessment exclusive of protocol violators (Per protocol analysis). Primary analysis will be on observed datasets, secondary on data including imputed variables.

8.3.1 Primary end point

Difference in mobility as measured by total SPPB score at 4 months between treatment arm ("comprehensive geriatric care") and standard care will be analyzed by use of ANCOVA.

Baseline ADL, I-ADL, CDR, gender, age, living alone, place of residence , type of fracture, length of stay, baseline muscle strength and preoperative waiting time will be explored as controlling variables in the analysis.

If there is a difference in SPPB between groups after 4 months, we will perform a second analysis on the effect of change in ADL/I-ADL, cognitive function (CDR, MMS and GDS) on SPPB by longitudinal ANCOVA combination approach[34].

8.3.2 Secondary end points

i) Mobility 1, 4 and 12 months

a) SPPB difference at 1 and 12 months between groups analyzed by ANCOVA

b) Difference in TUG between groups after 1, 4 and 12 months by longitudinal ANCOVA combination approach.

c) Difference in Gaitrite score after baseline, 4 and 12 months by longitudinal ANCOVA combination approach.

ii) Place of residence

Difference in place of residence after 1, 4 and 12 months will be analyzed by cox proportional hazard method.

iii) ADL

We will measure change in Barthel score at 1, 4 and 12 months and analyze it by longitudinal ANCOVA combination approach.

iv) iADL

Change in Nottingham score at 1, 4 and 12 months will be analyzed by longitudinal ANCOVA combination approach.

v) Cognitive function

a) Change in CDR after 4 and 12 months will be analyzed by longitudinal ANCOVA combination approach.

b) Change of MMS after 1, 4 and 12 months will be analyzed by longitudinal ANCOVA combination approach.

c) Change in GDS after 1, 4 and 12 months will be analyzed by longitudinal ANCOVA combination approach.

vi) Quality of life

Change in score EQ- 5d and difference in score at 1, 4 and 12 months depending on allocation will be analyzed in longitudinal ANCOVA combination approach.

vii) Patient /proxy satisfaction

The results of PasOp will be analyzed by ANCOVA comparing the 2 groups.

We will analyze whether there is a change in satisfaction after the control group (orthopedic department) moved from old to new department (prespesified subgroup).

viii) Health economy

Total cost at discharge will be calculated for each group and compared by ANCOVA with preoperative waiting time as a prespesified covariate. Both costs at date of actual discharge and date of “ready for discharge” will be published.

We will calculate costs from the municipalities as described in 6.7 for three time periods, from discharge to 1 month, from one month to four months and finally from four to twelve months and compare the two groups by longitudinal ANCOVA.

ix) Fear of falling

a) FES-I data from 1, 4 and 12 months will be analyzed in a longitudinal ANCOVA combination approach.

b) Score from the 4 item Likert scale will be analyzed in longitudinal ANCOVA combination approach.

x) Pain

a) The data from the questionnaire will be analyzed with a longitudinal ANCOVA combination approach.

Type of fracture, surgical complications, ability to walk and surgeon's opinion about immediate postoperative stability will be included in model.

b) Charnley hip score and NRS will be analyzed longitudinal ANCOVA combination approach.

9. Report

9.1

i) All results will be published in peer reviewed international journals according to the Consort 2010 criteria.

ii) When publishing tables, type of data (observed or imputed) will be specified in the tables.

10. SAP Amendments

Copies of all forms used in collecting datasets, a table of baseline variables and cost categories will follow the analysis plan as amendments.

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