Femoral Neck Fractures Treated with Hemiprosthesis: Comorbidity, Organ Affection and Bone Cement

On the quest for factors affecting mortality

Thesis by
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I Preface

I have always told my residents and students that in order to enjoy orthopedic surgery you have to enjoy working with elderly people. They constitute the majority of the orthopedic population. I regret to say that our achievements at times are not honored in line with more prestigious medical fields like heart conditions and cancer. I also regret that elderly suffering femoral neck fractures rarely enjoy backing from patient organizations and research founding. Most of all I regret the fact that elderly people fracturing the femoral neck suffer mortality in line with heart attack and stroke. I sincerely believe that we have the knowledge to improve the results for these patients. I refuse to accept that a femoral neck fracture initiates a decline of physical and mental capacity without our unconditional struggle and attention. We are obligated as health care providers to implement every available bit of knowledge in order to hinder our elderly population from suffering an unworthy departure from life.

Over 300 patients are included in our study making the basis of this thesis, 18 percent did not survive the first 90 days and 26 % did not make it through the first year. This work is dedicated all patients suffering a femoral neck fracture. Most of all it is dedicated to the one patient I will never forget. This lady was 92 years when she fell and broke her femoral neck. A long and physically active life reflected her understanding of the importance of movement. Her personal postoperative rehabilitation protocol contained physical activity as the only option. At three months follow up, she was walking without aid and scored 100 on Harris Hip Score. She had only one question; “When can I play volleyball again?” This lady was blessed with a physical health above average, but her question seemed to reveal some cognitive impairment. My first assumption was right, the second one as wrong as it could be. I realized this a few years later when my patient appeared as one of the main characters in a television documentary featuring a local volleyball team of elderly women that enjoyed the life of team sport. Her spirit and understanding of physical activity as an essential basement for quality of life should be an example and an inspiration for all of us.

II Acknowledgements

Without the visionary and decisive leadership of Tore K Kristiansen (Elverum) and Amund Rudlang (Drammen), this work could never have been carried out. The uncompromised financial and personal support from doctor Tore K Kristiansen has been crucial and admirable. His patience during the years collecting data and writing my thesis, deserve my unconditional respect and it is highly appreciated. Collaboration with The Norwegian Hip Fracture Register resulted in paper four. This joint venture was crucial. The hospitality, impressing scientific skills, enthusiasm and clinical mindfulness of Professor Lars B Engesæter, dr Tarjei Vinje, dr Jan Erik Gjertsen and statistician Valborg Baste was an inspiration for the present work.

The creative mind behind the CNC study in Drammen and Elverum was dr. med. Ola E. Dahl, he was the study leader, and my supervisor through all the years. His dedication towards this study and my thesis, his energetic enthusiasm towards science in general and his ability to impatiently drive projects forward has been astonishing, admirable and in periods demanding. In spite of his work load, Ola has never once missed a call or neglected questions; he has supervised my work with empathy and ownership way beyond reasonable expectancy.

The CNC study group (Picture 1) started inclusion of patients in 2004. The effort shown by my good colleague doctor Fredrik Hjelmstedt was essential to initiate the study. The database, engineered by Vladimir Milich, made data collection possible in a structured way and at the same time made the information easily accessible. The support and enthusiasm by our secretary in Drammen, Yvonne Bell, and the meticulous patient follow-up by our study nurse in Elverum, Eli Lundemo Øieren, was of great value with respect to data collection and data quality.

The statistical work has been patiently supervised by dr. philos Are Hugo Pripp, his skills can not be overestimated nor can his pedagogic abilities. Ares pleasant and warm personality was comforting and of great inspiration.

Picture 1. The CNC- Study Group outside the Thrombosis Research Institute, Chelsea, London. From left: Eli Lundemo Øieren, Ove Talsnes,Tore K Kristiansen, Thor Arne Valle, Are Hugo Pripp, Yvonne Bell, Ola E. Dahl, Vladimir Milich, Amund Rudlang and Fredrik Hjelmstedt.

Professor Olav Reikerås has been the formal university representative and the main supervisor during my work with this thesis. Olav has a remarkable experience with orthopedic science. His skills cover the entire field of orthopedics. His comments, questions and suggestions have brought the work forward with improvements of quality as well as presentation.

To my orthopedic colleagues in Elverum I want to express my deepest respect for constituting a team of hard working surgeons that makes every day an inspiration. A special thank to my assistant chief dr Helge Wangen for inspirational discussions and for his appreciated ability to cover my even unexpressed requests necessary to fulfill this work.

I wish to thank all doctors and nurses that have been involved with collection of data in Drammen and Elverum hospitals during the CNC study program. Likewise, I am grateful for the excellent service supplied by the librarians at the hospital library in Elverum and Hamar.

The orthopedic departments in Elverum and Drammen financed the practicalities of the CNC program and my chief Dr. Tore K Kristiansen sponsored most of the time needed to finalize this thesis. In addition, I received a donation from Sykehuset Innlandet Hospital Trust to cover some of the running expenses. Ortomedic AS sponsored our CNC- Study Group meetings. These professional conferences inspired the entire staff and kept us going. The involvement of Thor Arne Valle has been of great importance for me and the entire CNC group and I am deeply honored for the Charnely grant I received from Ortomedic foundation.

My initial ambition was to make this project invisible for my family, this failed completely. The support and understanding from my wife and best friend Siri, have always been crucial in order to realize my ambitions. I am forever grateful to you. I will also thank our sons Vebjørn, Vetle and Olve for making every day different; some days have been challenging, always unpredictable, frequently exhaustible and unconditionally hilarious. Most of all they have daily reminded me what really matters in life and have supplied the navigation I needed in order to realize the importance of this undoubted fact.

III List of Abbreviations

ALAT	alanine aminotransaminase
ASA	American Society of Anesthesiologists
BICS	bone cement implantation syndrome
CHD	coronary heart disease
CK	creatine phosphokinase
CK-MB	creatine phosphokinase isoenzyme M and B
CNC	cemented non-cemented study
C3a	complement component 3a
C5a	complement component 5a
DCH	Drammen community hospital
ECG	electrocardiogram
ECH	Elverum community hospital
ELISA	electrochemiluminescence immunoassay
eGFR	estimated glomerular filtration rate
FCF	fractura colli femoris
FNF	femoral neck fracture
γ-GT	gamma-glutamyl transpeptidase
HRR	hazard rate ratio
Ig E	immunoglobulin E
IMP	intramedullary pressure
IU	international units
kPa	kilo Pascal
µmol/L	micromol per liter
MMA	methylmethacrylate
MRI	magnetic resonance imaging
NNH	number needed to harm
PaO_2	partial pressure of oxygen in arterial blood
PVR	pulmonary vascular resistance
RCT	randomized controlled trial
RR	relative risk
SBHF	Sykehuset Buskerud Hospital Trust
SIHF	Sykehuset Innlandet Hospital Trust
SMR	standardized mortality ratio
SVR	systemic vascular resistance
TF	tissue factor
U/L	units per liter

IV List of Publications

I Clinical and biochemical prediction of early fatal outcome following hip fracture in the elderly
Talsnes O, Hjelmstedt F, Dahl OE, Pripp AH, Reikerås O.
International Orthopaedics 2011; 35:903-907.

II **Biochemical lung, liver and kidney markers and early death among elderly following hip fracture**
Talsnes O, Hjelmstedt F, Dahl OE, Pripp AH, Reikerås O.
Arch Orthop Trauma Surg 2012; 132:1753-1758.

III **No difference in mortality between cemented and uncemented hemiprosthesis for elderly patients with cervical hip fracture**
A prospective randomized study on 334 patients over 75 years
Talsnes O, Hjelmstedt F, Dahl OE, Pripp AH, Reikerås O.
Arch Orthop Trauma Surg 2013; 133:805-809.

IV Perioperative mortality in hip fractured patients treated with cemented and uncemented hemiprosthesis: a register study of 11,210 patients
Talsnes O, Vinje T, Gjertsen JE, Dahl OE, Engesæter LB, Baste V, Pripp AH, Reikerås O.
Inernational Orthopaedics 2013; 37:1135-1140.

V General Introduction

Hip fracture / femoral neck fracture
A hip fracture is any fracture involving the proximal femoral bone of which 3 subgroups are defined (Figure 1); the femoral neck fracture (also referred to as a cervical fracture, intracapsular fracture or fractura colli femoris (FNF)), the intertrochanteric fracture and finally the subtrochanteric fracture. These fractures involve different anatomic locations; the femoral neck (respecting the boundaries of the femoral joint capsule), the trochanteric area or the subtrochanteric part of the femoral bone. Fractures involving the femoral head are not recognized as hip fractures, but rather looked upon as an independent entity of the femoral bone fractures, often differing from the hip fractures in aetiology and treatment.

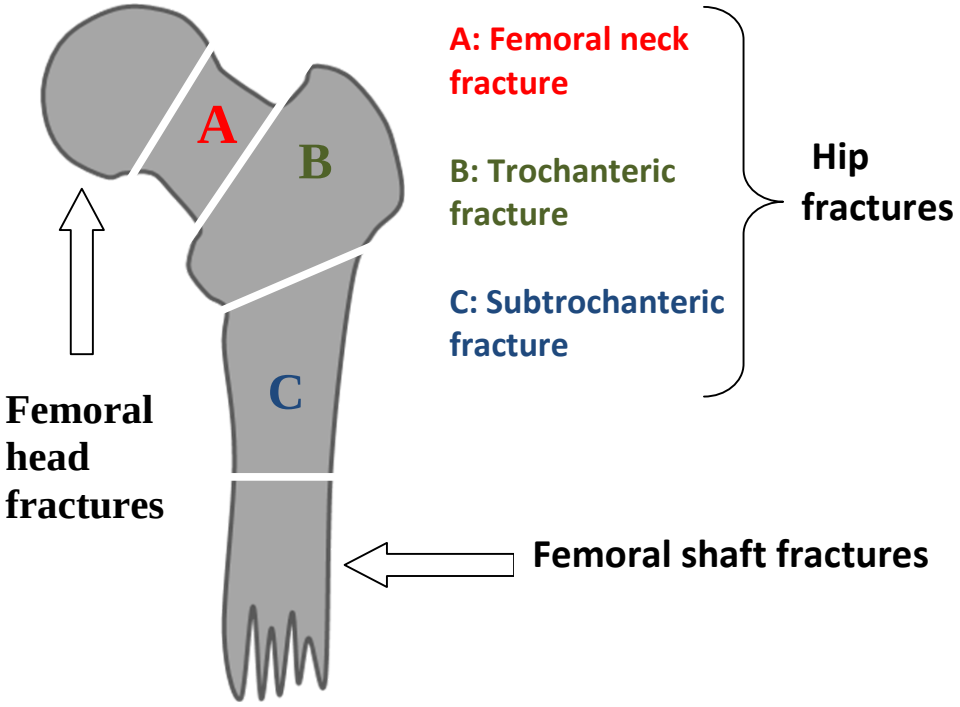

Figure 1. Proximal femoral fractures according to anatomical localization. Exact demarcation between the fracture types differ slightly in the literature and complex fractures certainly do not respect such schematic boundaries.

The femoral neck fractures constitute the majority of hip fractures in Norway. Nearly 60 % were neck fractures in 2014 (1), differing only slightly from figures the previous decade. Studies on proximal femoral bone fractures do not always distinguish between the fracture types and might deal with hip fractures as an entity. This applies primarily to scientific work on epidemiology, mortality/morbidity and functional outcome whereas studies on treatment certainly distinguish the subgroups due to different treatment strategies depending on the anatomic location of the fracture (Figure 2).

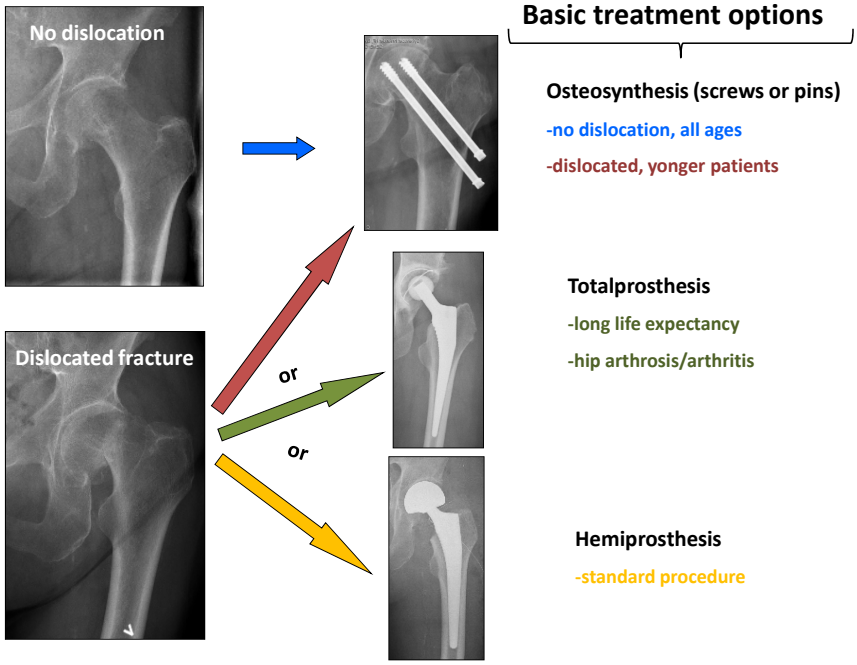

Figure 2. Basic treatment options for femoral neck fractures with and without dislocation (Garden classification 1-2 vs 3-4). Indications for the different procedures differ between surgical departments both nationally and internationally.

Hip fracture incidence

The incidence of hip fracture is high throughout the world. The highest incidence ever reported was in Oslo, Norway in 1996/97 (2). From 1999 to 2008 the incidence in Norway decreased by 13.4% in women and 4.8% in men (3). This shift is not confirmed internationally where estimates lack consistency (4;5). Even though the incidence of hip fractures may decrease, the longer life expectancy will increase the proportion of elderly (6;7). Consequently, we face an upcoming international epidemic of hip fractures challenging the health care system.

Mortality / morbidity

Most studies on mortality and morbidity handle hip fractures as an entity and femoral neck fractures are often not accounted for separately.
The hip fracture is a life threatening injury with a 6 month mortality of 11-23% and a one year mortality of 22-29% (8). The average patient suffering such a fracture lives for another 5 years (9). The over all mortality seems to be unchanged in Norway between 1978 and 1997 (10), this parallel international figures between 1959 and 1998 (8). Few studies have presented recent secular changes in mortality. A relatively small retrospective cohort of 487 patients by Schneppendahl (11) reported a decrease in mortality between 1989 and 2009. The standardized mortality ratio (SMR) was 1.21 the last period (2006-2009) indicating an only slight increase in mortality compared to the background population. The decrease in mortality was more pronounced for men and younger patients than for women and older patients. A British study (12) by Klop gives no indication of improvement in mortality the first decade this century; even though the mortality has decreased for hip fracture patients, this only reflect the general decrease in the age matched non fractured population.We face this disappointing fact in spite of improved awareness towards the preoperative procedures, treatment regimes and rehabilitation protocols for hip fracture patients. Different models for reducing mortality and morbidity are developed and results from orthogeriatric ward projects have been promising with regard to morbidity and function (13), but not accordingly so for mortality (14). Many of the survivors suffer from pain and functional limitations, some struggle with activities of daily living and are in need for more help to cope with daily routines. For many patients the hip fracture represents a turning point towards less independency and consequently a disseminating quality of life (15-17).

Treatment of femoral neck fractures

During the last decade the treatment regime has changed for femoral neck fractures. All fractures have historically been treated with osteosynthesis. Over the last decade there has been a shift towards treating dislocated fractures with prostheses (Figure 3). The reason for this change in practice was due to numerous reports on high reoperation rates with screw fixation compared to hemiarthroplasty (18-21). Uncemented hemiarthroplasties have gained popularity as compared to cemented hemiprosthesis, a trend that seemed to peek in 2012. Totalarthroplasties also show an increasing trend as a treatment option for hip fractures, over 92% of these prosthesis were implanted due to femoral neck fractures (22).

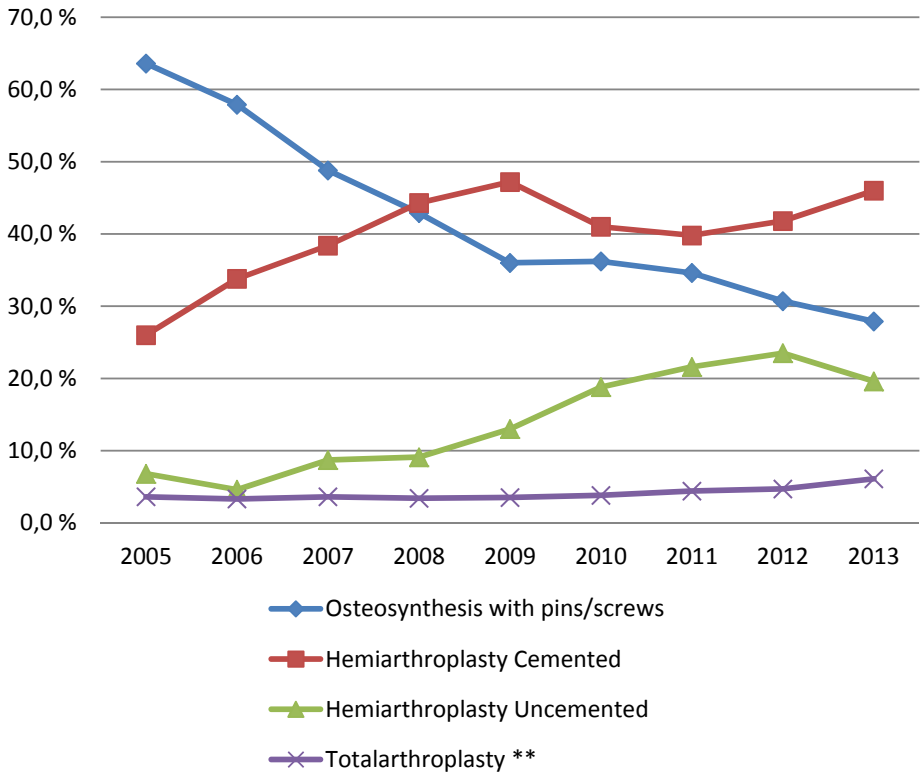

Figure 3. Treatment trend of femoral neck fractures in Norway based on the Norwegian Hip Fracture Register Report 2014(22)
** This is the amount of totalarthroplasties for hip fractures during the period; nearly all are implanted due to FNF (92.8%).

Mortality risk factors

In spite of improved treatment strategies, follow-up regimes and rehabilitation protocols; the mortality following hip fractures have not decreased significantly the last decade. In order to improve the outcome after hip fracture repair we need to identify the patients at risk. Numerous risk factors have been proposed. They can be divided into 2 main categories; patient related and treatment related factors (Table 1). The factors are listed according to when the risk is exposed in the chain of treatment, and weather it is modifiable or not. Several of these factors are preventable and modifiable whereas others are genetic and leave us with few preventable measures. Some of these factors are preventable before the fracture occurs and challenges the quality of the primary medical care supplied by the general physician.

Searching along the chain of treatment for hip fractured patients, risk factors are identified all the way from the living room where the fracture occurred, into the hospital, through the preoperative phase, the peri and postoperative period, and through the entire rehabilitation period. This involves rehabilitation facilities, retirement facilities and the patient pre and post fracture residence. Table 2 summarizes many of the studies describing significant risk factors affecting mortality among hip fractured patients. Table 1 and 2 show the enormous variety of risk factors, several are well documented whereas others only describe weak associations.

The studies summarized in this thesis have mainly concentrated on pre-existing and exposing risk factors associated with fatal outcome.

Table 1. Mortality risk factors for elderly hip fractured patients

Treatment related factors		
Preoperative	high pulmonary pressure(23;24), postponed surgery(9;25)	
Surgical treatment	timing of surgery(26-29), cementation(30), surgeons experience(31), cement preparation(32), choice of implant(33), duration of surgery(23;34), conservative treatment(9), perioperative fracture(35;36)	
Postoperative	postoperative infection(37), additional hospital admission(37-39), postoperative dependency(37), bedridden(9), prosthetic dislocation(40), subsequent fracture(41), dosage of antithrombotic agent(9), cardiac complication(9), stroke(42), delirium(37)	
Rehabilitation	physical therapy(43-45), multidisciplinary intervention(46), high intensity resistance training(47), receiving home care(48;49)	
Patient related factors		
	Modifiable	***Not modifiable***
Laboratory findings	low albumin(38;50), low hemoglobin(50), low leucocytes(51;52), low E-GFR(53;54), high troponin(33;38;52), high creatinine(55;56), low natrium(57)	
Physical fitness	general walking ability(27), walking aid outdoors(58), not walking outdoors(39;59), low physical functioning(58), low handgrip strength(57), poor ADL(60)	
Medication		diuretics(42), increased intake of prescription drugs(38), >4 prescription drugs(42)
Social status		living alone(33;40;57;61), living in a nursing home(60)
Patient characteristics	BMI ≤ 20(9;23;27;38;42;57;62;63)	advanced age(9;23;27;33;38;39;42;57;60;62;63), male gender(60), heart rate > 100(63), high Risk Mortality Index(60), Barthel Index ≤ 18/20(33)
General health/diseases	pneumonia(27;38;57;64)	high ASA(57), diabetes(57), cancer(33), previous myocardial infarction(33), chronic pulmonary disease(42;58;63), > 2 chronic diseases(9;39;57;58), reduced mental status(38;42), dementia(42;57;60), cardiac disease(23;40;42;59), more comorbidities(48)

Table 2. Studies showing significant mortality risk factors for elderly hip fractured patients.

Author/year(ref)	Study Design (n)	Diagnosis		Age	Mortality risk factors		
		HF	FNF		Patient related factors	Treatment related factors	Follow up
Kieffer et.al /2013(49)	R (585)		X	84	S-albumin <35g/dl		1 year
Pimlott et al /2011(54)	R (583)	x		65+	low S-albumin		in hospital
Spurrier et.al /2011(53)	P (108)	x		60+	↑ in Troponin-T from admission		1 year
Fisher et.al /2008(37)	P, Cohort (238)		X	60+	↑ mortality when cTroponin I ≥1µg/l		in hospital
da Costa et.al /2009(65)	R (184)	x		65+	♂ bedridden postopr., ♀ total dependency postopr., postopr hospital admission	♂ physical therapy protective	1 year
Bhattacharyya et.al /2002(39)	R, Reg (43215)	Orthopaedic surgery		all	chronic renal failure, congestive heart failure, chronic obstructive pulmonary disease, hip fracture, age>70		in hospital
Alegre-López et.al /2005(58)	P, Cohort (218)	x		50+	poor mental status, limited function, institution dependency at discharge, male gender		1 year
Meyer et.al /2000(26)	P, CC (248)	x			↓ mental status, >2 chronic diseases, not walking outdoors preoperatively, ↓ handgrip strength		3 ½ years
Hossain et.al /2012(43)	R (1402)		X	79-94		cemented hemiprosthesis	In surgery death
Halbert et.al /2007(46)	SR,I (2177)	x				↓ mortality when multi-disciplinary rehabilitation	3-12 months
Singh et.al /2012(25)	P,I(124)	x		80		mortality ↓ 81% for intervention group with high intensity progressive resistance training and	12 months

						targeted multidisciplinary treatment	
Simunovic et.al /2010(36)	SR/MA (4208)	x		60+		mortality ↓19% when early surgery	1-12 months
Westberg et.al /2013(35)	P (184)		X	80		47% vs 21% mortality when periprosthetic infection	1 year
Duckworth et.al /2012(55)	P(2718)	x		25-94	Dementia, diabetes and S. Aureus are independent predictors of mortality following deep infection	↑ mortality when deep infection	30 days
Hagino et.al /2013(30)	R (512)	x		60+	hyponatremia (Na<135 mEq/L) at admission was independently associated with in hospital death		In hospital
Ames et.al /2010(31)	R Reg	x		81.8		↓ mortality for experienced (high volume) surgeons	1,3 and 12 months
Leidinger et.al /2002(24)	PRC (72)	x		81		Vacuum mixed cement reduced the mortality to 2.8% compared to 13.8% in the control group. Preoperative pulmonary pressure >30mmHg ↑mortality	not stated
Holt et.al /2010(32)	Reg (4284)		X	50+		Postponement without correction of medical abnormality before surgery ↓ mortality	1 month
Avery et.al /2011(62)	PRC (81)	x				Less mortality for totalarthroplasties vs. hemiarthroplasties for displaced intracapsular fractures.	9 years
Haentjens et.al /2010(50)	MA		X	50+	↑mortality for older people and men		3 months 1,2,5,10 yrs
Bhaskar et.al /2011(33)	R (791)		X	60+	Hb 80-100g/l and Lymphocyte count ≤ $1.1x10^9$ on admission ↑mortality		1 year
Eiskjær et.al /1991(61)	R(204)	x		54-96	↑mortality for patients from nursing		6 months

					home, with chronic pulmonary disease, pneumonia, creatinine level >1.7mg/100ml, previous myocardial infarction, male gender and long duration of surgery.		
Harris et.al /2010(64)	P(666)		X	65+	↑mortality for nursing home patients		1 and 12 months
Holvik et.al /2010(44)	P(567)		X	65+	↑mortality for nursing home patients, and when ASA score ≥ 3		1 year
Gregersen et.al /2010(57)	I(211)	x		65+		Interdisciplinary geriatric intervention among nursing home residents ↓ mortality	1 and 3 months
Hu et.al /2011(40)	MA/SR (64316)	x		Mean >80	Advanced age, male gender, nursing home/fascility living recidence, poor walking capacity, poor ADL, high ASA, poor mental state, multiple comorbidities, cognitive impairment, diabetes, cancer and cardiac disease predicts excess mortality		1 month – 5 years
Kammerlander et.al /2011(51)	R	x		80+		Excess mortality for patients with more comorbidities, subsequent fractures and admitted from nursing home facility	3 years
Nitsch et.al /2009(47)	R	x		75+	Estimated GFR<45ml/min/1.75m^2 ↑ mortality		7.25 years (mean)
Rhame et.al /2010(52)	R(11326)		X	65+		↑ mortality for patients not receiving home care	3 months
Singh et.al /2008(60)	R		X		High preoperative creatinine and low eGFR associated with ↑ mortality	Low postoperative eGFR associated with ↑mortality	1 month
Juliebø et.al /2010(38)	P(364)	x		65+	Use of diuretics, history of coronary		21 months

					heart disease, male sex, Barthel index≤ 18/20, heart rate >100 at admission and body mass index ≤ 20. The use of statins shown to be protective regarding mortality.		
Bjørkelund et.al /2009(27)	P(428)	x		65+	↑ mortality risk for patients with ASA ¾, age>85 years, male sex, dependency in living, dementia diagnosis, more than 4 prescribed drugs, Hb<100g/L and creatinine >100µmol/L		4 months
Costa et.al /2011(28)	Reg (16496)		X	60+	Male sex, ASA scoree , age and walking accompanied outdoors are accociated with ↑ mortality	↑ mortality when cementing	At discharge
Costain et.al /2011(41)	Reg (25739)		X	All ages		↑mortality for cemented monoblock hemiarthroplasty	1 day
						↓mortality for cemented monoblock hemiarthroplasty	1 week, 1+12 months
Heidari et. al /2012(45)	Reg (255841)		X	All ages		Half dose low molecular weight heparin thromboprophylaxis ↓ mortality	In hospital, 1 month, 1 year
Fisher et.al /2006(9)	P, I (961)	x		60+		↓ mortality for intervention group with combined orthogeriatric care from 7.7 to 4.7 %	4 year
Petersen et.al /2006(23)	P(1186)		X	♀83 ♂81	Cardiac complications, dementia,male sex, advanced age, waiting time before operation and stroke ↑ mortality	Dislocations of the prosthesis and perioperative fracture ↑ mortality	3 months
Shoda et.al /2012(34)	Reg (80800)		X	60+	Male gender, advanced age, high number of comorbidities, and delay over 5 days are associated with ↑ mortality	Conservative treatment ↑ mortality	In hospital

Dedovic et.al /2011(63)	R,P (66)	x		65+		↓ mortality for patients with high cardiac risk when treated operatively compared to conservative treatment.	1 and 5 months
Libero et al /2012(42)	Reg (56500)	x		60+	↑ mortality for older patients, male gender, high chronic morbidity, high Risk Mortality Index		In hospital
Tarazona-Santabalbina et.al /2012(59)	R (1363)	x		69+	↑ mortality for single patients, patients with increased intake of prescription drugs, patients with complications, high co-morbidity score, male sex, cognitive impairment, high age, delirium and history of heart failure		1,6 and 12 months
Koren-Hakim et.al /2012	R (215)	x		65+	Poor nutritional status is associated with ↑ mortality, but only comorbidity and low functioning can predict mortality		36 months

Abbreviations. R: retrospective study, P: prospective study, Reg: register study, I: intervention study, MA: meta-analysis, SR: systematic review, PRC: prospective randomized controlled study.

VI Background for the study

In 2003 the orthopaedic department at Elverum Community Hospital changed the treatment regimen for femoral neck fractures from cemented hemi prostheses to an uncemented standard procedure (Landos Corail stem, Depuy, Warshaw, IN, USA). During the first 15 months following this shift of procedure, we prospectively registered complications and fatalities at the 3 months follow-up. When comparing the same number of consecutive patients before and after the change of practice, 4 fatalities were found in the cemented group and none in the uncemented group (66). Post mortem examinations were not done. No obvious relation between these mortalities or reason for the difference between the groups was found, although the patient records and death certificates were scrutinized.

At the same time a similar change of practice was initiated at the orthopaedic department in Drammen. A trial program based on historical data and research by dr. Dahl prompted collaboration between the departments. The aim was to explore factors influencing mortality in elderly that underwent femoral neck fracture repair with hemi-prostheses i.e. cement fixed and non-cement implanted stems (The CNC study). Three main questions were asked:

1. Could intraoperative deaths and fatalities occurring in close proximity to surgery be linked to the use of cement for anchoring the hemiprosthesis?
2. Which organs are affected and related to mortality?
3. Can we identify predisposing risk factors associated with mortality?

1. Cementation

The use of cement has been controversial ever since it was introduced to orthopaedic surgery more than 50 years ago. Sudden intra-operative deaths have repeatedly been described in the literature (67-71). The “bone cement implantation syndrome” (BCIS) has been a frightening complication to cemented procedures throughout the history of prosthetic joint surgery. The sums of clinical signs and symptoms have been given several names i.e. Bone Cement Implantation Syndrome (BCIS), fat embolism syndrome, microembolism syndrome. The syndrome has also

been focused on by anesthesiologists, this attention is due to intraoperative morbidity and mortality and has led Donaldson and co workers to propose a definition and classification of BCIS (72). In addition a milder form of BCIS, resulting in postoperative hypoxia and confusion, is proposed from the same group.

The clinical features of BCIS are primarily cardiopulmonary and include hypoxia (73;74), hypotension (74-76), cardiac arrhythmias (77), increased pulmonary vascular resistance (PVR) (76-80), and cardiac arrest (71;77;78;81-85). These clinical findings usually appear at one of five stages during the surgical procedure; femoral reaming (86-88), femoral or acetabular cement implantation (81), insertion of the prosthesis (83;87-90) or joint reduction (89). Much is known about the mechanisms behind this syndrome (72), and substantial experimental and clinical research has presented a number of theories explaining the physiological and biochemical changes initiated by the cement (91).

The monomethylmethacrylate theory.
Bone cement consists of two main components, liquid monomer and polymer powder. The monomer refers to the molecule of methylmethacrylate (MMA) which is polymerized when the components are mixed. This exothermic reaction reaching up to 120°C (92) leaves a small fraction of the monomer unpolymerized. This residual monomer is absorbed into venous blood (93;94) and the half life of this residual monomer is about 2 minutes. Experimental studies has shown the monomer to be lipophilic and show affinity to myelin sheaths, intracellular membranes and plasma membranes (95). The monomer also accumulates in blood cells and is cytotoxic in sufficient amounts (96;97). The toxicity of the monomer is clearly evident, but weather the concentration of residual monomer is sufficient to induce this cytotoxicity in vivo or even cause detectable organ dysfunction is not proven (81). The physiological impact of MMA is thoroughly investigated and certainly evident, and there is reason to believe that the possible clinical consequences are more likely to appear in patients with reduced physiological reserve capacity and marginal organ functions. Elderly people suffering femoral neck fractures are patients possibly vulnerable for the physiological challenges induced by the bone cement.

The cell aggregates and embolism.
Acute trauma and orthopedic surgery to large bones initiates intravasation of bone marrow cells (75) containing tissue factor (TF)(98;99). TF activates thrombin and triggers activation of coagulation in veins draining the surgical field (86), in addition procoagulant debris, cell aggregates and microparticles are brought to the lung vessels (90). The lung capillaries play a key role in cellular interaction, entrapment and further thrombin generation (100). Impaction of bone cement adds mechanical and chemical trauma, this escalates the coagulation process (86;88;101), trigger hemodynamic instability intra operatively, and favor cardiorespiratory and vascular complications.

The femoral reaming produces bony fragments or debris (75;81) capable of entering the venous system from the femoral shaft. At the same time droplets of fat (82) and air (102) follow the same route representing emboli entering the heart through the right atrium, to the right ventricle and the pulmonary artery before final distribution in the microvasculature of the lung. During the cementation and impaction of the prosthesis considerable pressure is produced, and the risk for emboli is even greater. In addition methylmethacrylate (MMA), cement particles (77) and aggregates of platelets and fibrin (75) are squeezed into the circulation. The intramedullary pressure (IMP) produced by introducing the femoral stem is considerably higher for cemented implants compared to uncemented prosthesis and the experimental work by Orsini and co-workers suggests that the IMP generated by uncemented implants is not associated with hemodynamic alterations (81). The IMP of uncemented prosthesis is also increased during opening of the medullary canal, broaching and insertion of the femoral stem. The peak pressure is dependant on the surgical technique and modifications have been introduced in order to decrease the pressures involved (103;104). The IMP is much higher during cemented procedures and cementing techniques have changed primarily to reduce the IMP involved and minimize the risk of significant bone marrow release (105). The threshold for clinically detectable hemodynamic alterations due to increased IMP still remains to be established. The variability of several patient related factors such as cardiopulmonary reserve capacity might indicate that this threshold is individual. Approximately 25 % of the population have a patent foramen ovale (106) and are susceptible to emboli entering the arterial circulation targeting any end organ including the brain. Another transit route into the arterial circulation is directly through the pulmonary circulation. The different emboli just described are shown to pass the

pulmonary vasculature and represent direct microemboli physically entering the arterial circulation. Paradoxal embolization through a venous-to-arterial circulation shunt has been proven to cause cerebral embolization (107).

The extent of these emboli has been visualized using echocardiography, showers of emboli are detected in the right atrium, right ventricle and in the pulmonary artery (108;109). Magnetic Resonance Imaging (MRI) has detected cerebral fat emboli after arthroplasty (110;111) and highly echogenic and mobile emboli are detected by transoesophageal echocardiography ranging up to 5 cm in length (108). Transcranial Doppler has also detected cerebral fat and air emboli during hip fracture surgery (107;112;113).

Postmortem studies have demonstrated the pulmonary embolization just described and histological studies have identified fat droplets and bone marrow debris as well as polymethylmethacrylate microembolies in the lung (77). The emboli just described initiate cascades of events not only locally in the affected bone, but also in the lung vasculature and in target tissue. These cascading events are shown to initiate cardio respiratory alternations representing a threat to any patient, more so for those patients suffering marginal reserve organ capacity (114).

Respiratory depression, reduced oxygenation and hypotension are key findings for cemented patients as opposed to those receiving uncemented implants (81;87;115). The occurrence of these clinical findings correlates in time with the emboli following increased IMP induced by cementation and prosthesis impaction (81). The showers of pulmonary emboli induces hypoxia and right ventricular dysfunction leading to hypotension (76). These changes are not necessarily proportional to the embolic load (87;108). The emboli initiate several mechanisms besides mechanical obstruction of the pulmonary circulation facilitating an increase in pulmonary vascular resistance (PVR). Mechanical damage of the endothelium induces a vasoconstriction and release of endothelial mediators. Simultaneously procoagulant mediators such as thrombin and tissue thromboplastin/tissue factor directly increase PVR and indirectly via other mediators (75;116). Systemic vascular resistance (SVR) is also reduced due to tissue factor, 6-keto PGF 1α (76;78) and secondary mediators such as adenine nucleotides (75).

Surgical interventions, creating a distal venting hole, aimed to reduce the IMP during cementation have shown significant pressure reduction. This procedure represent a possible prophylaxis preventing emboli formation from air, blood, cellular debris, cement particles and bone from entering the circulation due to high IMP (117;118). This procedure has not been implemented into prosthetic surgical guidelines and is not done routinely during surgery today.

Although the embolic model is thoroughly documented we know that embolization not always induce hemodynamic changes (87;109;115) and the degree of embolization correlates only scarcely with the extent of hypotension and hypoxemia (75;109). Embolic events are tolerated well by most patients and studies have failed to show perioperative changes in the ventilation perfusion ratio (87). Even though embolization is recognized as part of the explanation of BCIS other mechanisms are likely to co exist.

Hypersensitivity theory.
The clinical similarities of BCIS and anaphylaxis gave rise to the idea of a histamine mediated explanation of the cardiopulmonary affection. This theory was based on studies showing significant increase of plasma histamine among patients experiencing hypotension during cementation (119). Weather this effect was due to a direct effect of the monomer or indirectly mediated through IgE is not known. H1 and H2 antagonists seemed protective against cardiovascular reactions although these results failed to be reproduced. Contact (Type 4) hypersensitivity to MMA is known among hospital personnel (120), but this can not explain cardiopulmonary changes related to the cementation of the prosthesis.

Complement activation theory.
Activation of the complement system (increase in C3a and C5a levels) has been demonstrated in patients undergoing cemented hemiarthroplasty and not so for uncemented patients (121). The anaphylatoxins C3a and C5a are potent mediators of vasocontriction and bronchoconstriction. The release of anaphylatoxin and oxygen desaturation appear to be prevented by methylprednisolon (119). The activation of the complement system has been studied more recently, but complement activation was not identified (79).

Multifactorial theory.
A number of physiological reactions are initiated by the use of bone cement and through the cementation procedure. Some of these reactions occur immediately during the surgery and initiate life threatening cardiopulmonary alterations while other reactions are delayed and induce late complications. We know that the plasmatic cascade systems are affected by the procedures we perform in the operating room. This include alteration in the coagulation system, the fibrinolytic system and the complement system, additionally vascular cells are affected. Monomethylmethacrylate (MMA) induces local, regional and systemic reactions challenging patients undergoing cementing procedures. Some of the reactions previously described culminate with a clinical sign or symptoms while other reactions are balanced by the physiological reserves and remain subclinical. Cementing and MMA are undisputedly responsible for adverse reactions. The pathophysiology is well described for some of these reactions, other reactions are still not fully characterized and yet others are possibly still unknown. Individual variations in physiological reserve capacity and individual differences with regard to the preexisting comorbidities makes the complete picture blurry and challenges our ability to handle each patient as individuals. Accounting for this individuality a multifactorial etiology certainly seems plausible.

2. Organ affection
The fragility of elderly patients is usually expressed by malfunction of one or more organs; heart, lung, liver and kidney are frequently affected. Hospitalized patients are clinically and biochemically routinely examined for and frequently monitored for any malfunction or derangement in these vital organs. The clinical staffs at hospitals are familiar with and focused on this follow-up of elderly patients and knowledge of any association between organ affection and mortality could be vital in the treatment and survival of this group of patients.

Biochemical markers associated with mortality after hip fractures among elderly people can help us to identify patients at risk shortly after admittance to the hospital. The parameters chosen are Troponin, CK and CK-MB for the heart, ALAT and γ-GT for the liver, Creatinine for the kidney and PaO_2 for the lung. These parameters are selected based on availability, previous experience using these parameters, general acceptance as organ specific parameters, simplicity/standardisation with respect to analyzing process and prompt availability of the results at the hospitals involved. When these studies were planned CK-MB still was

used as an indicator for myocardial tissue damage, but has been replaced by Troponin-I and Troponin-T as myocardial muscle strain indicators. The method for measuring and the boundaries for normality for Troponin have changed over the years although not within the period covered by this study. The strengths of using these parameters are depicted by the 5 reasons for selecting them, all parameters certainly also have weaknesses as representative parameters for each organ.

Heart

The excess mortality following a hip fracture is dominated by cardiovascular events and heart related conditions, this is also shown in autopsy studies. Such studies are rarely done today and accordingly not performed in our studies (62;122-128). Myocardial injury is difficult to diagnose because of impaired patient communication, limitations of clinical manifestation and non-specific electrocardiographic (ECG) changes (129;130). The isoenzyme CK-MB is expressed in the myocardium and CK in the skeletal muscle cells. These two enzymes have traditionally been analyzed in plasma to distinguish myocardial injury and skeletal muscle injury (53;131). Troponin have proven to be more specific and sensitive to cardiac injury (126;132-135), for this reason Troponin is today the most commonly used cardiac muscle strain indicator. Release of Troponins into the circulation is considered to reflect coronary heart disease (CHD) and Troponin I is also shown to predict death and first CHD event in men free from cardiovascular disease (136). Three variations of this intramuscular protein is known (I,T and C) and they are important mediators of muscle contraction working along with Calcium. Heart muscle injury will induce a leakage of the different Troponins into the circulation making them prone to detection as quantitative determinators of cell damage. Increased plasma level of Troponin has also been reported in pulmonary embolism, septicemia and following major orthopedic and cardiac surgery. In these conditions high plasma Troponin levels have been associated with severe adverse outcomes and increased mortality (31).

Liver

A femoral fracture followed by surgery is a challenge affecting most organs and vital functions. Even though the trauma itself rarely produce any mechanical or morphological damage to the organ, the functional capacity of each organ certainly often is challenged, and more so for elderly suffering marginal premorbid organ functions. The liver is such an organ, and even prior to the fracture the liver might possibly be

debilitated by polypharmacy, in addition the ageing liver is vulnerable to medication (137;138). A hospital stay related to a femoral neck fracture even complicates this picture by introducing additional medication connected to pain relieve, anesthesia, thromboprophylaxis and postoperative follow up. Monitoring the liver is done routinely in any hospital, and by using the enzymes alanine amino transaminase (ALAT) or gamma glutamyl transpeptidase (γ-GT) important information can be obtained by familiar parameters.

Kidney
Insufficient kidney function is related to inferior prognosis for patients admitted to hospital regardless of the reason for admission (139). We know from Bhattacharyya`s study (65) that inpatient deaths following orthopedic surgery is highly related to kidney function. Chronic renal failure and acute renal failure are highly and significantly associated with an increased mortality risk preoperatively and postoperatively. It has been postulated that acute deaths might be patient related and that late death and death associated to complications might be related to the hospital treatment (140). Re-admission of patients is related to increased mortality, and from a recent study by Kahn and co workers (141) we learned that as much as 18.2% of these re-admissions were caused by renal failure or dehydration. This illustrates the importance of correcting these factors during the hospital stay and even during the postoperative period, following hospitalization.

Lung
Postoperative pulmonary complications are one of the major concerns regardless of the cause of hospitalization among elderly. Pulmonary derangement account for a major share of both complications and mortality following femoral neck fractures (60;142-144).
The gas tension of oxygen measured in arterial blood (PaO_2) is a semi quantitative estimate measuring the grade of lung failure, and gives important information on the functional capacity of the lung.

3. Predisposing mortality risk factors
The identification of predisposing risk factors would give us a tool to identify the patients at risk immediately as the patient fractures the femoral neck. By labelling these susceptible patients early in the treatment chain we will be able to customize the treatment and follow-up regimen for fragile and marginal patients. Identification of patients at risk will visualize the patients in strong need for reducing negative factors

affecting mortality and focus on those improving survival. Therefore we asked the following two questions;

1. Could we, by the use of easily obtainable information, identify patients at risk for early mortality following a femoral neck fracture?

2. Is there reason to believe that cementing procedures can explain mortality differences?

VII Aims of the study

The aims of this study were:

1. To identify organ related risk factors for early fatal outcome for elderly patients suffering femoral neck fractures and treated with hemiarthroplasty.

2. To explore the impact of cementation on the mortality of patients undergoing hemiarthroplasty following a femoral neck fracture. In addition we sought to evaluate predisposing and exposing risk factors of fatal outcome.

VIII Materials and methods

Prospective study
Three hundred and thirty four patients with dislocated femoral neck fractures were prospectively included from two local community hospitals in Drammen (SBHF Drammen (BCH)) and Elverum (SIHF Elverum (ECH)) in Norway. The patients were randomized into cemented (Landos Titan, Depuy, Warshaw, IN, USA) or uncemented (Landos Corail, Depuy, Warshaw, IN, USA) hemiprostheses.

The biomechanical function (modular and bipolar) and design (identical shape) of the two prostheses were similar which left cement the main difference between the methods. The eligible patients were consecutively enrolled and blindly randomized by the surgical nurse on call as the patient entered the operating room. Prefabricated non transparent and sealed envelopes (clusters of 10) contained the note deciding either a cemented or none cemented procedure. The envelopes were made by an external secretary otherwise not involved in the study. They were treated according to the routines at the local hospital and the patients were operated by the attending resident surgeon, sometimes together with a consultant surgeon depending on the experience of the resident surgeon at call.

The main endpoint was mortality, secondary endpoints were; organ affection estimated by organ specific biomarkers (blood samples), peri and postoperative blood loss, transfusions and operation time,
We included the oldest part of the population, those over 75 years, assuming this being the most debilitated part of the hip fracture population and consequently representing the most common challenges met by health care system. The patients were followed during the hospital stay and evaluated with an outpatient follow-up at 3 and 12 months postoperatively. Thromboprophylaxis (low molecular weight heparins) was routinely administered preoperatively (on hospital admission) with dalteparin 5000 IU s.c (ECH) or enoxaparin 40 mg s.c (BCH) and subsequently once daily for about one week. Postoperatively the patients were mobilized by physical therapists and nurses according to individual needs and discarded to a rehabilitation facility or back home depending on their ability to cope with the individual demands of daily living.

With this prospective randomized design we could evaluate the impact of cement on mortality. Additionally, by using the whole cohort we were able to evaluate organ affection related to death regardless of fixation method.

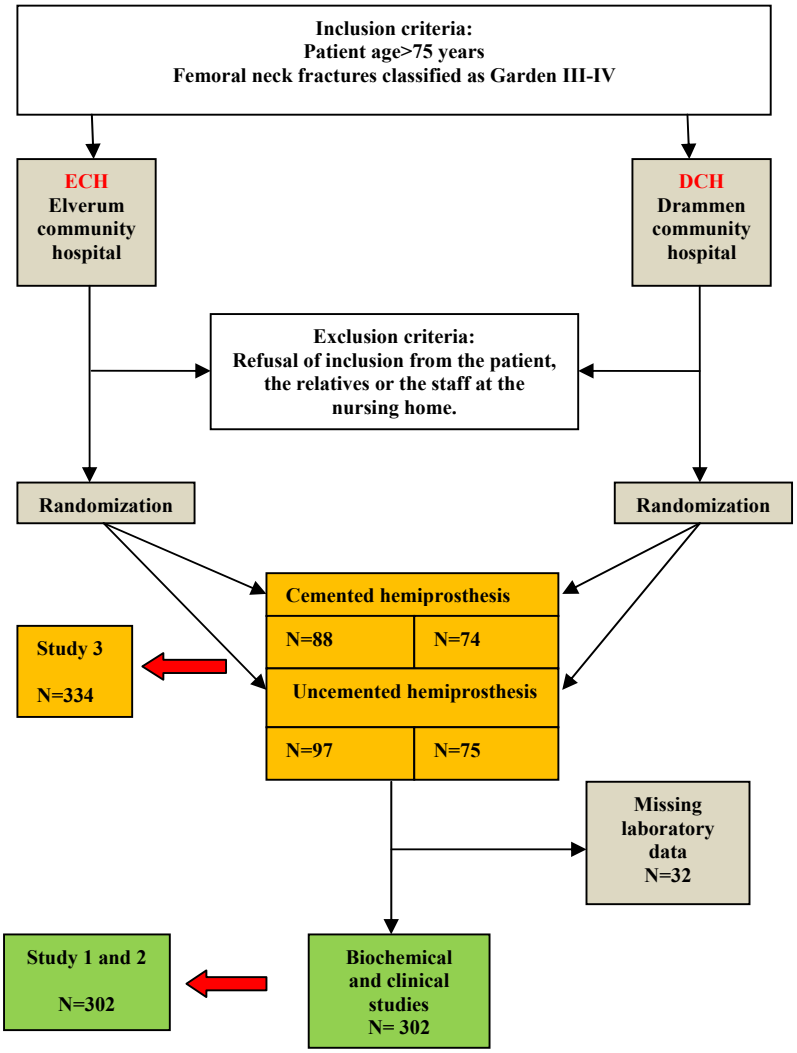

Figure 4. Flow chart over patients included in study 1-3

Necessary legal acceptances were applied for and accepted by due authorities. The study was registered in ClinicalTrials.gov (NCT00800124, CNC2008). Written informed consent was obtained and regarding patients with cognitive impairment, the Ethical Committee

accepted inclusion unless this was refused by the relatives or the nursing home personell.

Register study

Based on previous studies analyzing mortality, we suspected a marginal difference in mortality figures between the methods in our randomized study. By analyzing a national register cohort we were given the opportunity to supplement our prospective randomized study (334 patients) with national register data dealing with the same groups of patients during a 6 year period (over 11000 patients). Such a large number of patients gave us the opportunity to focus on the immediate postoperative period as well as the long term postoperative period with respect to mortality differences. Every hospital in Norway conducting hip fracture surgery reported to the Norwegian Hip Fracture Register. The register contain data from the patient, the fracture and the operation (145). Mortality data were obtained from Statistics Norway.

Comorbidity

Comorbidity as an important risk factor for mortality is an established fact (146). The question remains which comorbidity score system to choose for this group of patients. We have chosen ASA simply based on practicality, logistics and availability (147;148). The ASA grading system (1-5) is based on how a systemic disease affects the patient; 1: healthy, 2: mild systemic disease, 3: severe systemic disease limiting activity, 4: systemic disease being a constant threat to life and 5: moribund patient not expected to survive 24 hours.

Statistics

Descriptive statistics were mean or standard deviation or number of patients or percentages. Differences between mortality groups were tested using two-sample *t* test or Chi-square test for continuous or categorical data, respectively. Non-parametric Mann-Whitney tests were done for TnT due to skewed distribution. A linear mixed model for repeated measurements with a random intercept and Bonferroni adjusted pair wise post hoc comparison were used to analyze the organic biochemical markers (ALAT, g-GT, PaO_2 and creatinine) with respect to mortality and repeated venous blood analysis. Univariate and stepwise multivariate logistic regression analysis were used to estimate unadjusted and adjusted

odds ratios with respect to survival at the 3-month follow-up. Results from multivariate logistic regression were based on models including only significant terms from stepwise regression to maximize the number of patients included. Missing data were assumed to be completely at random and the significance level was set to $p<0.05$.

We used Poisson regression to estimate risk ratio (RR) at the day of operation and Cox regression to estimate RR of mortality during follow-up for patients with cemented versus uncemented prostheses.
In Paper 4 adjustments were done for potential confounders such as comorbidity (ASA score), age, sex, dementia and time interval from fracture to surgery (intervals 0-6, 6-12, 12-24 and 24-48 hours) in univariate and multivariate models. We found the risk factors influencing mortality to be different the day of surgery (day 0) and the first postoperative day (day 1) as compared to the rest of the follow-up period. Due to this difference, the mortality estimates were done separately for these periods. The number needed to harm (NNH) is the number of cemented prostheses implanted in order to experience one fatality caused by the cementation alone. The NNH was estimated according to different ASA scores. Analysis with Kaplan-Meier curves and log-rank test between the groups were also performed.

All statistical analyses were conducted using PASW (IBM, Armonk, NY, USA), version 18 was used in Paper 1-3, and version 19 was used in Paper 4.

Blood sampling
Blood samples were obtained from an antecubital vein, collected preoperatively (-1), postoperatively (within 24 hours (0)), on days one (24-48 hours (+1)) and four (+4), PaO_2 was measured preoperatively, and at 1, 6 and 24 hours postoperatively (Table 3). The blood samples were immediately processed and analyzed according to local laboratory routines.

Table 3. Blood sampling schedule, estimated in hours/days after closure at surgery.

Variables	Preoperative (-1)	Postoperative			
		0-24 hours (0)		24-48 hours (+1)	4 days (+4)
Hb	X				X
Troponin	X	X		X	X
CK	X	X		X	X
CK-MB	X	X		X	X
ALAT	X	X		X	X
γ -GT	X	X		X	X
Creatinine	X			X	X
PaO_2 *	X	1 hour	X		
		6 hours	X		
		24hours	X		

* PaO_2 was measured through an arterial sample (radial artery). All other blood samples were from venous blood (antecubital vein).

Laboratory analyses
Troponin T (TnT) and CK-MB were measured by electrochemiluminescence immunoassay (ELISA, Roche, Basel, Switzerland and Abbott, Abbott Park, IL, USA). Values for TnT were only measured at the ECH study centre (n=146). The arterial blood gas samples (PaO_2) were immediately processed according to local laboratory routines and were analyzed by visible absorption spectrometry (ABL 700 Radiometer AS, Copenhagen, Denmark). These measures were done at 1, 6 and 24 hours postoperatively. ALAT, γ-GT and creatinine were measured by absorption photometry (ROCHE, Basel, Switzerland and Abbott, North Chicago, IL, Chicago, USA). Hemoglobin concentration was analyzed preoperatively (day -1) and on postoperative day 4 (CellDyn 4000/Sapphire, Abbott Diagnostics, North Chicago, IL, USA).The laboratories and equipment at the hospitals involved are certified according to national and international standards and meet all the criteria set for laboratory analysis involved in our studies.

The blood loss was measured during surgery in the suction drain. In addition the sponges were weighted (1g=1ml). Blood was collected

postoperatively in wound drains and the volume was recorded until removal of the drain the first postoperative day. Transfusion requirement was decided on the discretion of the surgeon.

IX Ethical considerations

For both studies involved; written informed consent was obtained. Demented or cognitively impaired patients could be included unless relatives or nursing staff refused inclusion. For the register study this has little or no consequence for the patient since there is no optional treatment regime, the data are handled with discretion and patients are anonymously entered in the database. The prospective study involves blood samples, randomization between two treatment regimes and extra controls at 3 and 12 months. Both treatments are internationally accepted and recognized treatment options with only marginal differences regarding surgical trauma, morbidity, mortality and complication rate (149). Extra controls and possibly extra blood samples are certainly an additional burden for the patient. This can on the contrary represent an extra safety measurement and secure a follow up otherwise not effectuated. For some debilitated and institutionalized patients these controls could represent a troublesome experience involving nursing home staff otherwise needed at the institution. Considering the severity of the prognosis for this group of patients and the need for more information in order to cope with the challenges involved; the extra burden is evaluated to be within an acceptable range.

X Papers

Paper I

The main objective of this study was to investigate the significance of certain clinical and biochemical parameters with respect to mortality within 3 months postoperatively in elderly suffering a femoral neck fracture. Just over 300 patients above 75 years operated with a hemiprosthesis were followed consecutively at two community hospitals in Elverum and Drammen (Norway). Information on age, sex and comorbidity assessed with the American Society of Anaesthesiologists (ASA) score was obtained before surgery. The muscular enzyme Creatine Kinase (CK), myocardium-specific Creatine Kinase (CK-MB) and the heart muscle specific enzyme Troponin-T (TnT) were analyzed from venous blood and collected at 4 timings; preoperatively, within 24 hours postoperatively, at one and four days postoperatively. Troponin-T was analyzed only at one hospital. Multivariate analysis showed that age, male sex and comorbidity correlated with mortality at 3 months ($p=0.027$, $p=0.002$, $p<0.001$ respectively).

Muscular enzyme analysis showed that surgery induced a 2-3 fold increase of CK and CK-MB, this did not correlate with mortality. Elevated TnT levels (>0.04µgram/l) correlated strongly with death before, one day and four days after surgery ($p=0.003$, $p=0.005$ and $p=0.003$, respectively). When adjusting the Troponin-T analysis for sex, age and ASA-score the correlation to mortality at 3 months was confirmed at day 4 postoperatively.

In conclusion; for elderly patients undergoing femoral neck fracture surgery, information on age, sex, comorbidities (ASA) and laboratory analysis on the cardiac specific enzyme Troponin-T provide the clinician with useful information on patients at risk for early fatal outcome.

Paper II

The same group of patients as described in paper 1 was assessed in order to describe the association between organ dysfunction and 3 months mortality after surgery.
Blood samples on liver (alanine aminotransaminase (ALAT) and gamma-glutamyl transpeptidase (γ-GT)), lung (PaO_2) and kidney (Creatinine) function were collected before and after the surgery.

We found a positive correlation between the plasma levels of ALAT, Creatinine and death, and an inverse relationship between PaO_2 and death. When controlling for important confounding factors described in paper 1 (sex, age and comorbidity) we found ALAT and creatinine levels to be significantly and independently related to fatal outcome at 3 months postoperatively.

In conclusion; the results provide the clinician with information on organ dysfunction in patients undergoing hip fracture surgery. We suggest a stronger emphasis on monitoring and correcting these functions when possible.

Paper III

Impaction of bone cement is a mechanical and chemical trauma that adds to the reaming and broaching of the bone marrow. It contributes to the substantial local and systemic thrombin generation. Several reports have indicated bone cement as the immediate trigger of cardio respiratory and vascular dysfunction, occasionally fatal, and described as the bone cement implantation syndrome. In spite of this knowledge, bone cement is widely used for prosthesis fixation, possibly due to the lack of clinical evidence supporting the basic science indicating bone cement as a mortality risk factor. Three hundred and thirty-four patients above 75 years were enrolled from two hospitals in Norway. This cohort includes the patients presented in paper 1 and 2. Patients were prospectively followed for one year and primarily randomized in two mechanically similar prostheses; one cemented and the other uncemented. Average age was 84 years, 75 % were female and 60% had symptomatic comorbidities (ASA score 3-4). No difference in mortality between the methods was found up to 1 year postoperatively. We did find reduced operation time and blood loss in the uncemented group, both findings were statistically significant.

In conclusion; uncemented hemiprosthesis implanted in elderly due to a femoral neck fracture showed benefits with regard to shorter operation time and less bleeding, but did not seem to influence 1 year mortality compared to cemented implants.

Paper IV

Based on numerous reports on perioperative deaths for patients undergoing cemented hip arthroplasties we wanted to focus our quest for mortality risk factors on the immediate postoperative period. Power analysis suggested that around 10000 procedures were needed in order to achieve safe calculations, giving the mortality difference would be of clinical interest. Such a number of patients were reported to the Norwegian Hip Fracture Register, and our data is based on 11210 cervical hip fractures reported to the register between 2005 and 2012 (8674 cemented and 2536 uncemented procedures). Significantly increased mortality the day of surgery and on the first postoperative day was found in the cemented group. This finding was robust even after adjusting for independent risk factors such as age, sex, cognitive impairment and comorbidity (ASA score). For the first post-operative day the number needed to harm was 116 (one death for every 116^{th} cemented hemiprosthesis). For the most comorbid patients (ASA score 3 and 4) the number needed to harm was 33.

In conclusion; the mortality risk was significantly increased for cemented hemiprosthesis the day of surgery and the first postoperative day compared to uncemented procedures. This increased mortality risk was closely related to patient comorbidity estimated by the ASA score of the patient.

XI General Discussion

Methods

The first three studies are based on the CNC study as described earlier. The CNC study on displaced femoral neck fractures was ambitious and covered many aspects of fnf including; demographics, treatment modalities, radiological findings, patient satisfaction, biochemical measurements, hemodynamics, mortality, morbidity, medication, pain, function and quality of life. The protocol of the study involved doctors and nurses all through the treatment chain at the hospital. The number of measurements was challenging, therefore, in order to avoid additional workload for the staff involved with the study, only well known and familiar measurements were included. The organ parameters selected for the biochemical measurements were similar to the parameters used in the daily clinical work primarily to make any finding applicable to our own patients. Some of the parameters are certainly not as specific as we wish for and other measurements could justify as better options, but familiarity and availability were the preferred selection criteria. For the kidney and lung function other available options were creatinine clearance and alveolar-arterial oxygen gradient respectively. These were certainly reliable and well known function scores for these organs, but not frequently encountered in our surgical ward and therefore not used in this trial. Using the ASA score as a comorbidity score is certainly not what it was intended for, and several other score systems including specific fnf comorbidity score systems have been developed, but the universal use of the ASA system across surgical fields for decades probably justifies its use as a reliable tool for this group of patients.

For the clinical trial (study 1-3) one could argue that the exclusion criteria introduce a selection bias. Based on numerous historical reports of intraoperative deaths combined with studies describing negative physiological effects from the cement and the cementing procedure, we suspected that the most debilitated patients (elderly with marginal organ functions) were at particular risk. Clinical experience over the years have

given us reason to believe that the use of cement possibly represent an additive challenge to already debilitated patients. Patients exposed to a hip fracture with a following surgical procedure face a physiological challenge. When suffering from marginal organ reservoir capacity some of these patients face challenges intensive care units repeatedly struggle hard to battle. The average age was about 84 years and a large portion of them suffered comorbidities and dementia possibly debilitated to such an extent that acceptance to such a study seemed too much of an effort. This could leave us with a cohort slightly less comorbid than expected. We have not included patients less than 75 years which is a relatively high age and this could compensate slightly for a lack of inclusion of the most debilitated patients.

In paper 3 we based the power analysis on historical intraoperative mortality data by Duncan (71), that had found about 12% death among cemented and none among uncemented hip fracture prosthesis operated patients, and 1 year mortality was historically reported as high as over 40% (150). We estimated that we needed to randomize between 200 and 350 patients (alpha 0.05(two sided) and power 80%). We decided to enroll at least 300 patients.

Results

Clinical characteristics as predisposing risk factors for mortality

In papers I-III, we evaluate different risk factors in the same cohort of patients. In paper I we use age, sex and ASA score to predict mortality at 3 months for hip fractured elderly patients. In order to make the results applicable to the general population at a community hospital we preferred to include patients over the age of 75 years. This high age correlate more with the average hip fractured patient than younger age groups. For the same reason we also wanted to include patients affected by cognitive impairment which also correspond well with the general hip fracture population.

We show that comorbidity evaluated by ASA score is an independent mortality risk factor. This goes for the immediate postoperative period as well as for the entire following postoperative period and is evident for both studies involved. Our assumption that ASA score is a reliable instrument for assessing comorbidity could be questioned; the system was initially developed as a preoperative risk assessment score by anaesthesiologists (151). Numerous score systems involving comorbidity are developed for clinical use and some are customized for hip fracture patients (152-155). Some of these score systems involve other factors such as age, gender, mental status and medication and do not isolate comorbidity as an independent risk factor. Even though the ASA score system was not intentionally a comorbidity instrument, it has been used as such based on its availability, simplicity and widespread international use in most surgical fields. The score system is easy to use both for anaesthesiologists and orthopaedic surgeons. The score is usually administered by anaesthesiologists securing the integrity and independency when used in orthopaedic studies, this advantage also applies to both cohorts constituting this thesis. The validity is debated, but the inter-observer consistency is within an acceptable range (156). Several studies have illustrated the usefulness of the ASA score in assessing intra and postoperative mortality risk, long time survival, morbidity, cost and length of stay (147;157). The ASA grading is also recommended as a useful tool assessing patients preoperatively in national recommendations for treating hip fracture patients (158).

Advanced age as a mortality risk factor is certainly well known and documented (62). Mortality among hip fractured patients is primarily due to circulatory diseases (159), closely linked to atherosclerotic processes reducing oxygenation of the tissues. The other main underlying causes of death for patients suffering from a hip fracture are respiratory diseases, malignancy and dementia. These diseases are accounted for when performing stepwise multivariate logistic regression analysis adjusting for comorbidities using the ASA score system. In spite of these adjustments, age is still an independent risk factor for mortality, and there are many reasonable explanations for this. Cells, tissues and organs degenerate by age, this ongoing process certainly might diminish tissue and organ capacity to fulfil optimal function and serve extreme needs when acute trauma and disease occur. Nevertheless this reduced organ function does not necessarily materialize in a disease detectable by the doctor or reflected through a comorbidity or clinical score system. Deficient reservoir capacity among elderly might therefore not become apparent, but could still represent a mortality risk factor expressed by ageing and insufficient subclinical tissue functionality. Several other factors due to ageing are depicted as possible and probable factors increasing the risk for mortality. Subclinical thromboembolic episodes increase as a result of different trauma and diseases and the control mechanisms of haemostasis degrade by time making organs more susceptible to derangement (160).

We show that gender also can predict mortality, and there still is a correlation with death even when performing adjusted analysis correcting for comorbidities and age. Males are more at risk for death when fracturing the hip than women (58;161-163). This applies not only to the prospective study, but also to the register study. Adjusted analysis show male gender to be a significant risk factor for death the first 3 months after the operation (paper I-III). For the register study males are at risk from day 2 postoperatively throughout the entire follow up period (up to 6 years). Gender does not show significance as a mortality risk factor at day one postoperatively being outranged through adjusted analysis by other risk factors like age, ASA score and cementation. This illustrates the fact that the different risk factors apply differently during the follow-up period. Our studies are not aimed at answering why men are at higher risk than women, but the question is certainly of great interest as well as important with respect to prevention, treatment and rehabilitation. Few studies are done investigating causes of death following hip fractures with respect to sex differences (164).

In article IV dementia as a risk factor is evaluated and proves robust from day 2 and through the follow up period even after adjusting for comorbidities, sex, age and cementation. At day 0 and 1 following the operation dementia or cognitive impairment is not a risk factor for mortality. This difference indicates that the same risk factor differs in impact according to the time from operation, and underlines the similar observation previously described for gender as a mortality risk factor. We find that within the first 48 hours postoperatively comorbidities evaluated by ASA score together with age are significant risk factors for death, dementia and gender are not. From day 2 postoperatively dementia and male sex are significant risk factors. The reason for this shift might indicate that different mechanisms causing death apply for these periods and that a different pathophysiological mechanism is challenged during the acute perioperative period. Our studies are not designed to reveal these factors, but the fact that risk factors have different impact through the postoperative period certainly opens interesting prospects for exploring mechanisms involved with early mortality after femoral neck fractures.

When evaluating dementia or cognitive impairment, definitions are paramount in order to compare results. In this register study dementia is evaluated by the surgeon based on the medical history of the patient and a brief investigation. This is certainly not a thorough evaluation, the diagnosis is complex and the acute circumstances involving pain, sometimes confusion, dehydration, malnutrition and delirium makes the diagnostic process even more complex. In spite of this complexity, dementia proves robust as a risk factor for mortality when evaluated as either no dementia, unsure or dementia. Based on the surgeon's evaluation, when no dementia is the reference, the relative risk for death is 1.63 for the unsure group as compared to 2.35 for the verified demented patients. These results are comparable to other studies outlining cognitive impairment or dementia as a significant clinical mortality risk factor (58;146). Based on these data the clinical evaluation done by the surgeon using the clock test (165) seems to be an easy, practical, fairly reliable and time-efficient instrument for evaluating possible cognitive impairment for elderly hip fractured patients.

When evaluating the mortality differences between cemented and uncemented implants, the rate of reoperation would be a factor worth considering given the fact that this group of elderly patients are vulnerable to repeated surgery and readmission (37). A study from

Gjertsen et al (166) on a similar group of patients as study 4 in this thesis shows an increased reoperation rate for uncemented implants (hazard rate ratios(HRR) 2.09). The reason for reoperations in the uncemented group were periprosthetic fracture (HRR 16.6), hematoma (HRR 5.3) and superficial infection (HRR4.6). There was no difference in one year mortality between the groups, but there might be different explanations for the short and long term mortality between these groups. Both periprosthetic fracture and infection are associated with increased mortality for this group of patients (36), More serious cardio-respiratory adverse event such as perioperative death, cardiac arrest were significantly more frequent in the cemented group again indicating different explanations for mortality depending on the time lap from fracture. These results are based on a register study with limitations regarding the similarity of the groups compared. In this study there was a significant difference in cognitive impairment ($p<0.001$) which we have shown is a predisposing factor affecting mortality for this group of patients. There was more cognitive impairment in the uncemented group indicating an overestimation of mortality for those patients. Anyhow, mortality might be affected by reoperation rate which seems more frequent in the uncemented group. To what extent this reoperation rate influence mortality on short and/or long term still remains uncertain.

Biochemical markers and their association with early mortality

Heart

By doing measurements preoperatively, during the perioperative period and postoperatively during the hospital stay we aimed at finding differences between Troponin levels for the patients that died within 3 months as compared to those surviving. The results are shown in Figure 4.

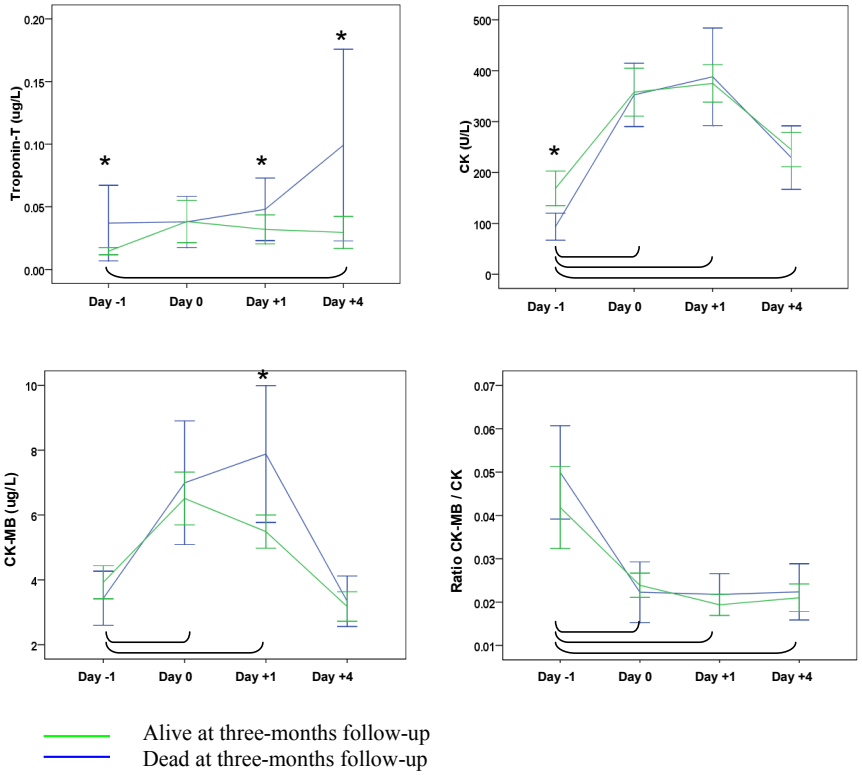

Figure 4. Mean and 95% confidence intervals for troponin-T, creatin kinase (CK), myocard-specific creatin kinase (CK-MB) and ratio of CK-MB and CK before surgery, perioperative and one and four days after surgery for three-months mortality.

Statistical significance ($p < 0.05$) between mortality groups is indicated by an asterisk (*). Statistical significant ($p < 0.05$) differences between before surgery and during follow-up are indicated by the connecting lines. *Day -1* day before surgery, *Day 0* within 24 hours after the operation, *Day +1* 24 – 48 hours postoperatively, *Day +4* four days after surgery.

In elderly, perioperative myocardial ischemia is often clinically silent without hemodynamic and notable ECG changes (167-170). Over the years, biochemical plasma markers have been used to distinguish myocardial injury from skeletal muscle damage, an approach also adopted in this study. Creatine Kinase, reflecting the general skeletal muscle trauma, increased perioperatively. This finding is in line with a recent study in elective hip replacement surgery (171). Possible heart muscle damage was in our study investigated with CK-MB and TnT analyses. We found small and inconsistent differences for CK and CK-MB plasma levels between those who died and those who survived. The ratio CK-MB to CK was decreased from hospital admittance (day-1) to day 0 and stabilized, indicating that skeletal muscle damage dominated and that any myocardial injury remained undetected. Logistic regression analyses showed no correlation with postoperative mortality. This analyzes suggest that CK and CK-MB are unspecific enzymes that not distinct skeletal and cardiac muscle damage following a hip fracture trauma and are not feasible as prognostic markers of mortality, a finding consistent with other investigators (172).

In our study we analyzed the heart specific Troponin T (only at ECH), and found that the plasma concentration was significantly higher on the forth postoperative day in patients that subsequently died compared to those who were alive. Patients with TnT levels above 0.04 μg/l had six times higher risk of dying compared to those with normal plasma levels. This calculation was robust when correction was done for age, sex and comorbidity (ASA score). These results fit with other reports that showed a second wave of Troponin elevation several days after surgery which correlated with postoperative mortality (133;173). As already outlined our results do not show any causality regarding mortality, only an association between Troponin T as an indicator of cardiac muscle affection and early mortality. As a response to our results indicating this association, Lippi and co writers (174) suggest a greater peri and postoperative emphasis on cardiac Troponins for patients undergoing major orthopedic surgery. A recent study from Hietala (175) and co-workers have also confirmed our results stating that elevated perioperative Troponin level is strongly correlated to mortality for this group of patients. The discrepancy between initial CK-MB rise opposed to the later increase in TnT at day 4 might be an indication of the superiority of Troponin as a cardiac specific marker. Troponins are not found in other than cardiac muscle tissue (176) whereas CK-MB even though cardiac specific will react on general muscle trauma reflected by

the fracture and secondarily by the following surgery. There is marginal difference between CK-MB and Troponin as an indicator (specificity and sensitivity) of acute myocardial infarction (177), but this goes for patients unaffected by musculoskeletal injury and surgery. Troponin-T was elevated at inclusion for patients that died; this could indicate that patients primarily affected by myocardial strain initiate the hospital stay with less reserve capacity to cope with surgery and rehabilitation.

Liver

We used alanin-amino-transaminase (ALAT) and gamma-glutamyl transpeptidase (γ-GT) as indicators for liver function and values were obtained preoperatively, perioperatively and at day 1 and 4 postoperatively (Table 3), values are shown in Figure 5.

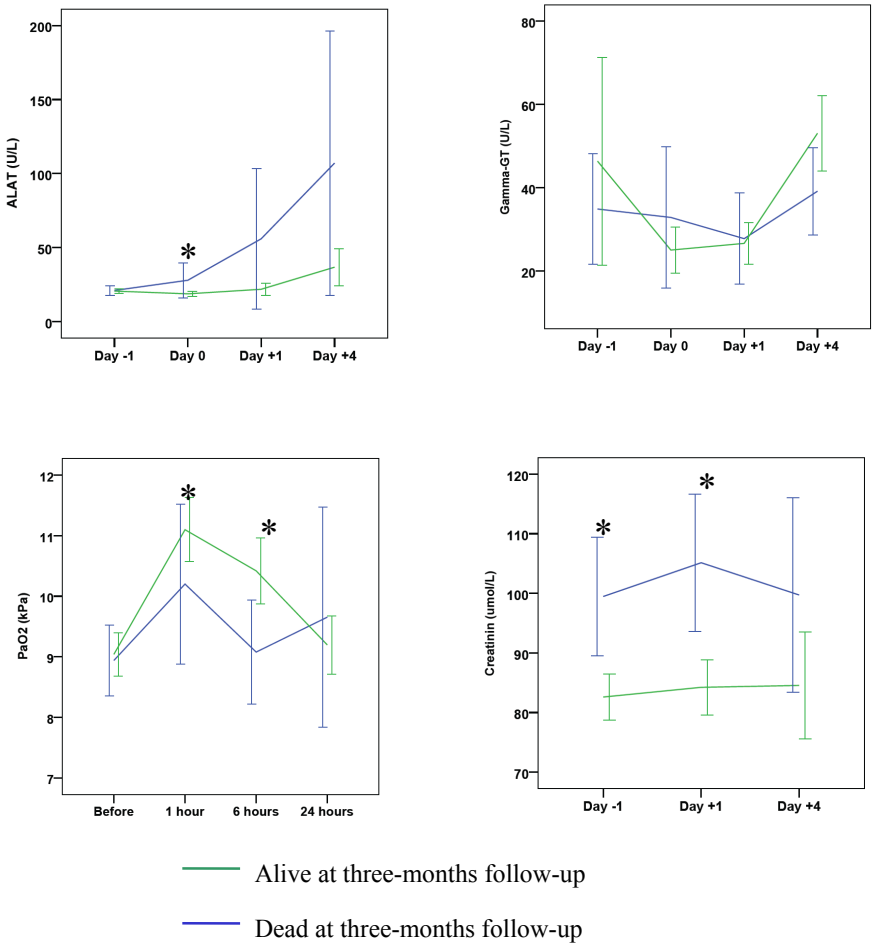

Figure 5. Mean and 95% confidence intervals for γ-GT, creatinine, ALAT and PaO_2 before surgery, perioperatively, one and four days after surgery for three-month mortality.
* Significant difference between biochemical markers for patients alive and dead after 3 months evaluated by independent sample T-test.

Liver affection is well known after orthopedic surgery and have been associated with administration of liver toxic compounds (137). Controlling for potentially confounding factors, we found that ALAT was an independent marker of fatal outcome. γ -GT did not show a similar correlation and accordingly did not prove valuable as an indicator for

liver affection related to femoral neck fractures. Although the mechanism of liver affection is uncertain, our data confirm previous studies and ALAT monitoring might add information worth considering in elderly undergoing hip fracture surgery. We find that the severity of liver affection, estimated by increased ALAT values stratified into quartiles, indicate a stronger association with mortality (Figure 6).

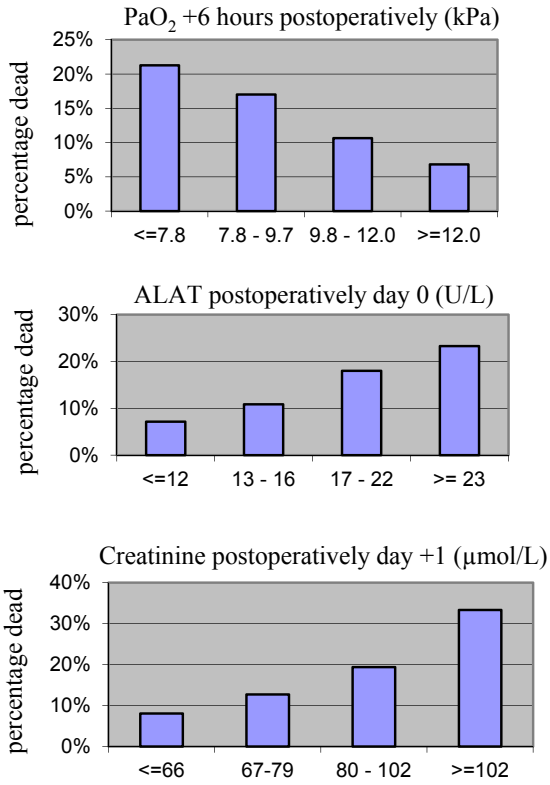

Figure 6. The relationship between perioperative biological plasma markers stratified into quartiles and death within 3 months after surgery. (p=0.034, p=0.016 and p=0.034 for PaO_2, ALAT and creatinine respectively).

Several possible explanations for this liver affection has been suggested as already mentioned, but our studies only describe a relation between

liver affection and mortality and do not answer these interesting and important issues. Weather this is due to the trauma and fracture, the surgery itself, medication or the immobilization, and weather the connection is due to a systemic reaction related to these factors remain unanswered although multifactorial etiology seems probable. This study does not provide any indication of a causal relation between the rise in ALAT and mortality.

Kidney

We found that kidney affection expressed by elevated creatinine level preoperatively and within two days postoperatively were associated with increased 30-day mortality for patients with femoral neck fractures treated with a hemiprosthesis. Adjusted estimates prove robust for the preoperative measures ($p=0.028$) while the postoperative analysis are only borderline none-significant ($p=0.058$). When estimating the mortality according to four increasing intervals of creatinine level we also found an increased mortality related to increased level of plasma creatinine concentration. This is strongly indicative of an association between renal function and mortality (Figure 6). Another interesting finding is that even though the creatinine level is within normal ranges it indicates an association with mortality. This might imply an inadequacy of creatinine as a predictor of mortality risk factor. Estimated glomerular filtration rate (eGFR) has been suggested a more accurate predictor estimating renal function for this group of patients (52). In a clinical setting a more accurate categorization of renal function among elderly might be needed in order to stratify mortality risk more accurately (178).

Causal relationship between mortality and elevation of creatinine is beyond the scope of our studies, but this has been and still is an ongoing discussion. We know from experimental studies that acute trauma and surgery trigger a thrombin activation initiating coagulation cascades possibly affecting organ function through microembolization which is associated with impaired functional capacity (179).We know that an increased level of creatinine might be related to dehydration. It has recently been shown that mild to severe dehydration is present in one third of the hip fractured population and that this finding is related to a quadrupled number of postoperative complications (180). Elderly people are often dehydrated at hospital admission and an increased focus on early operation might overrule our goal to correct dehydration preoperatively

and thereby contributing negatively to our aim of reducing complications and mortality (33).

Lung

We found a reduced PaO_2 at 1 and 6 hours after the operation, at 6 hours postoperatively the unadjusted measures showed borderline none significant difference between those who died and the survivors (p=0.056). Adjusted analysis also showed a difference, but again they were not significant (p=0.093). When stratifying PaO_2 into four quartiles we find over 20% mortality among those patients having a PaO_2 less than 7.85 kPa, and a mortality of just over 5 % for patients measuring a PaO_2 within normal range (Figure 6). This might indicate some co variation between reduced arterial oxygen tension and mortality for hip fractured elderly patients. Other studies have also shown this (73;90;181;182) and several explanations can justify the relationship just presented. From experimental studies in dogs (81) we know that PaO_2 has a marked reduction for cemented implants the first 60 minutes after implantation of the prosthesis, this does not apply for non cemented implants. Likewise, the peak IMP and the number of microemboli increase for all implants, but markedly more for cemented implants. Hemodynamic changes are also evident during insertion of the prosthesis. There is a rise in mean arterial pressure and pulmonary arterial pressure and this is also more prominent for cemented implants. Those animals demonstrating the highest mean IMP show a decrease in PaO_2 and an increase in mean pulmonary arterial pressure indicating a possible etiological explanation of hemodynamic changes and pulmonary affection. Embolic material from the bone marrow and venous blood (including debris and fat cells) detected in the pulmonary circulation is regarded as an indicator of the release of other tissue thromboplastic agents (75;90), causing fibrin trapping and platelet aggregation in the microcirculation of the lung. This might result in a release of smooth- muscle-active substances from the lung tissue giving rise to vasoconstriction and bronchoconstriction with a resulting decrease in PaO_2. The magnitude of this pulmonary insufficiency may depend on the severity of the trauma, the ability of the fibrinolytic system to clear the lung, the prophylactic anticoagulant treatment given and the individual cardiopulmonary reserve of the patient involved (183). The explanations just depicted are based on perioperative measurements, some of the changes are reversed shortly after surgery and do not necessarily explain postoperative pulmonary depression. We know that some of the mechanisms initiated during the operation are followed

by cascading events which add understanding to the pulmonary affection indicated by our studies. Clinical studies have shown deep vein thrombosis during the first week after the operation expressing an activation of the coagulation mechanism (184). Further studies also indicate that this is due to local activation of coagulation primarily as a result from bone traumatization during surgery (100). An activation of coagulation mechanisms locally and systemically is favoring thrombosis formation and thus contributes to reduced PaO_2 and compromised pulmonary function. Many of the studies that describe the pulmonary affection during prosthesis surgery are done on total hip arthroplasties due to arthritis as opposed to our studies performed on femoral neck fractures treated with a hemiarthroplasty. Both surgical procedures imply traumatization of bone during broaching, and both procedures imply an elevated IMP and squeezing of bone debris and fat locally into the venous blood during impaction of the prosthesis. There is good reason to believe that similar cascades of events are initiated by the surgeries involved in our study since the cascade of pathophysiological changes just described apply to the surgical manipulation of the femoral stem and to a much lesser extent to manipulation of the acetabular socket. To what extent the fracture itself, and the time lap from fracture to surgery affect the magnitude of procoagulant events is not thoroughly investigated, but could potentiate the detrimental biochemical changes previously discussed.

Cementation as a risk factor for mortality

In papers III and IV, cementation as a risk factor for mortality is evaluated through a prospective randomized study on 334 patients (Paper III), and by a register study (Paper IV) based on 11210 patients in The Norwegian National Hip Fracture Register. We find no difference in mortality between cemented and uncemented patients within one year postoperatively in the randomized study (HR 0.77, 95% CI 0.51-1.18, p=0.233). However there is a significant longer operation time (mean difference of 13 min, 95% CI 4-22, p=0.004) and perioperative blood loss (92ml, 95% CI 3-181, p=0.043) in the cemented group. In the register study we find significantly increased mortality the day of surgery and the first postoperative day in the cemented group (relative risk 2.9, 95% CI 1.6-5.1, p=0.001). This finding is proving robust even when adjusting for the most common individual risk factors such as age, sex, cognitive

impairment and comorbidity evaluated by ASA score. The increased perioperative mortality is closely related to comorbidity giving the number needed to harm (NNH) for the most comorbid group (ASA ≥ 3) is 33 (one death for every 33rd cemented prosthesis), compared to 116 for the less comorbide group of patients.

The results presented in paper 3 and 4 illustrate the fact that the mortality difference between the groups is marginal. Other studies have discussed this issue and have presented marginal and to some extent divergent results over the years (149;185-197). The Cochrane study by Parker et.al (149) concluded with no difference in mortality between the groups at any time period from up to 1 month through the third postoperative year. Most studies have investigated the mortality difference during the first month and later while few studies emphasize the immediate peri and postoperative period. Two register studies, parallel to ours, have recently done so. Costain and coworkers (28) reported from the Australian Hip Fracture Register increased mortality for cemented unipolar prosthesis the first day postoperatively, but failed to produced the same finding for bipolar implants used in our study. Similar results were reported from the British National Hip Fracture Database (27), but the endpoint of morality difference was estimated at discharge giving no attention to the immediate postoperative period.

We find that some of the common mortality risk factors act differently according to the time passing from the surgery. The first two days following surgery we find ASA score, age and cement to be significant risk factors for mortality whereas sex, cognitive impairment and time from fracture to operation are not significant risk factors during this period (Table 4). Following this initial postoperative period we find ASA score, sex, age, cognitive impairment and time from fracture to surgery to be risk factors as opposed to cementation which seems to be a risk factor only during the initial postoperative period.

Table 4. Risk and hazard rates at day 0 and day 1 combined and from day 2 postoperative to end of follow-up, respectively.

		Day 0 and day 1 combined				From day 2 postoperatively to end of follow-up			
Parameter		**Unadjusted**		**Adjusted***		**Unadjusted**		**Adjusted***	
		RR (95%CI)	**p-value**	**RR (95%CI)**	**p-value**	**RR (95%CI)**	**p-value**	**RR (95%CI)**	**p-value**
Fixation	Uncemented	ref		ref		Ref		Ref	
	Cemented	2.8 (1.6-5.1)	0.001	2.9 (1.6-5.2)	0.001	0.93 (0.87-1.0)	0.053	0.96 (0.89-1.03)	0.267
ASA (per 1 unit increase)		3.6 (2.7-4.8)	<0.001	3.2 (2.4-4.4),	<0.001	1.9 (1.7-1.9)	<0.001	1.58 (1.50-1.66)	<0.001
Age (per 1 unit increase)		1.1 (1.1-1.2)	<0.001	1.1 (1.1-1.2)	<0.001	1.06 (1.06-1.07)	<0.001	1.05 (1.05-1.06)	<0.001
Sex	Male	ref		ref		Ref		Ref	
	Female	0.9 (0.6-1.3)	0.635	0.9 (0.6-1.4)	0.676	0.61 (0.57-0.61)	<0.001	0.59 (0.55-0.63)	<0.001
Dementia:	No	ref		ref		Ref		Ref	
	Unsure	1.5 (1.0-2.2)	0.045	1.0 (0.7-1.5)	0.979	2.0 (1.8-2.2)	<0.001	1.63 (1.48-1.78)	<0.001
	Dementia	2.1 (1.3-3.3)	0.002	1.3 (0.8-2.2)	0.225	2.8 (2.6-3.0)	<0.001	2.35 (2.20-2.51)	<0.001
Time from fracture to operation (per 6h increase)		1.2 (1.0-1.4)	0.032	1.1 (0.9-1.3)	0.303	1.1 (1.0-1.1)	<0.001	1.03 (1.00-1.06)	0.026

* Values adjusted for other risk factors (age, sex, cementation, ASA-score, dementia and time from fracture to surgery).
RR: Rate Ratio. Cox regression analyses of data from day 2 postoperatively to the end of follow-up, it was statistically estimated as hazard ratio.

This finding indicates that the impact of important risk factors change during the postoperative period, and consequently the mortality risk should therefore be estimated for each postoperative day separately. Another possible consequence based on this finding could be that we face several physiological and biological factors causing these mortality differences, factors with different impact on mortality according to the time lap from surgery. Some of the risk factors might apply in relation to the surgery itself and represent a risk for the patient only for a short time span when the patient is highly vulnerable due to marginal reserve capacity. The most comorbid patients (ASA≥3), representing the most vulnerable group, are less susceptible to cope with the physiological demands such a patient is facing during surgery. Cement seems to be a risk factor during the initial phase following the operation and certain physiological factors are challenged due to the cement. We have shown in paper I and II that patients dying within 3 months show a tendency towards organ affection and dysfunction compared to patients that survive. This thesis does not evaluate the direct impact of the cement on perioperative organ dysfunction, we indicate a possible connection between the use of cement and organ affection. This theory needs further research in order to finally outline the pathophysiological factors explaining the increased mortality among the most debilitated patients. Cement as a fixation method of hip prosthesis was introduced almost 60 years ago and reports of early perioperative fatalities paralleled the development of the method (70;71;90;198-207). Few case review studies have addressed operative mortality with respect to fixation methods (77;87;208) and the incidence is estimated to 0.11% (72) in these non homogenous cohorts consisting of cemented hip patients. No patients receiving uncemented implants died during surgery in any of these studies indicating a causal relation between cement and intraoperative mortality. The intraoperative mortality for femoral neck fractures was 0.2% in the awarded study by Parvitzi consisting of hip prosthesis implanted between 1969 and 1997. Recent register studies have addressed this issue, Costa (27) reported mortality at discharge, concluding with no increase in perioperative mortality for cemented prosthesis and Costain (28) found a 1.7-times higher day-1 mortality for cemented monoblock prosthesis. We know from a cohort (166) similar to Paper 4 that 26 patients (0.3 %) died during surgery and 15 patients suffered a cardiac arrest (0.2%) while only one patient died (0.04%) in the uncemented group. This finding corresponds with the other studies, and clearly illustrates the importance of handling the immediate perioperative period separately when studying mortality. Most patients that died (23/27) were ASA score 3 or 4 which

underlines the assumption that debilitated patients are vulnerable subjects to the demanding pathophysiological mechanisms that appear during surgery.

Limitations

A register study certainly has limitations. The lack of randomisation indicate a careful approach when concluding, and such cohorts are certainly better instruments for creating a hypothesis than giving answers. Several biases appear and the selection of patient for the different treatments is certainly an important one. Some hospitals use only one method while others have recommendations for using another method. The experience of the surgeon and the timing of the operation could also differ between hospitals. Randomized controlled trials (RCT) can supply these answers giving the number of patients included is based on power estimates reflecting the minimal relevant clinical difference between the groups. In our randomized study the estimates of strength were based on studies that indicated mortality figures that were too high. This gave us a group of patients undersized in order to find mortality differences. A randomized trial large enough to find mortality differences probably would involve a large number of patients and conduction of such a study would be a challenge both to manage and to finance.

The RCT study was conducted at two local hospitals with limited experience organizing clinical trials of this magnitude. All doctors from the orthopaedic department and the entire nursing staff from the surgery department including the emergency, the operating theatre, the intensive care unit, the policlinic and the ward were in some way involved in the collection of data from the patients included in the study. This large scale involvement challenges the quality and quantity of data collection given the ownership to such clinical trials routinely decrease with time during the inclusion period.

XII Conclusions

1. Comorbid patients with ASA score 3 or more are at particular high risk of fatal outcome.

2. Cognitive impairment and time from fracture to surgery are risk factors for mortality from day 2 postoperatively.

3. Myocardial affection, estimated by elevated Troponin-T plasma level at day 4 postoperatively, is associated with increased early mortality within 3 months.

4. Plasma elevated Creatinine and ALAT consistent with reduced kidney and liver function are independent risk factors associated with fatal outcome .

5. There seems to be an indication of a dose related response between liver, kidney and lung dysfunction, and 3-month mortality.

6. There is an increased blood loss and increased operation time for patients operated with cemented hemiprosthesis compared to the uncemented prosthesis.

7. Cement is an independent risk factor for mortality the day of surgery and on the first postoperative day (<48 hours).

XIII Perspectives

The picture of mortality risk factors is complicated, and increasingly so as new factors are identified. Many patients are victims of complex risk profiles which constitute social, mental, physical, constitutional, environmental and medical factors. Some of the factors also apply only to one gender or a specific age group. This makes it paramount to obtain a thorough understanding of the risk factors involved through the entire treatment chain. As our knowledge expands we should use this on behalf of our patients in order to see the individual human being, and to a greater extent customize the treatment according to the risk factors involved for each individual patient.

The quality of our treatment and the patient safety is closely related to our ability to implement uniform guidelines when observing and treating this fragile group of patients. These guidelines are paramount in order to reduce mortality and morbidity.

The conclusions of this thesis outline a few risk factors which might improve the survival for some of the patients. Our future task should be to dig even deeper into the details and create structured data from large prospective cohorts which to an even greater extent can reveal risk factors related to the treatment and the follow-up protocols of these patients.
In order to improve morbidity and mortality we still need research related to preoperative planning, perioperative care and rehabilitation regimes.
We also need to use the existing data in the national registers to reveal hidden and important information about which patients die and why.
We have illustrated the fact that certain risk factors vary in importance according to the time-lap from surgery. This should be considered more thoroughly when mortality questions are investigated, especially in relation to the perioperative period.

Even more important, we need to perform research on prevention of hip fractures; the future prospect is depressing with an increased population of elderly people prone to hip fractures. This increase will apply to the developing counties which often lack health care systems capable to address this challenging world wide epidemic.

XIV Appendix

International Orthopaedics (SICOT)
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ORIGINAL PAPER

Clinical and biochemical prediction of early fatal outcome following hip fracture in the elderly

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Abstract Hip fracture, a moderate musculoskeletal trauma, is associated with a high postoperative mortality. Most patients are elderly, with comorbid conditions and often with heart disease. The objective of this study was to find out if clinical parameters and analyses of specific muscle enzymes could predict three month postoperative mortality. A total of 302 patients above 75 years of age with hip fracture were consecutively enrolled. Baseline information on age, sex and comorbidity assessed with the American Society of Anesthesiologists (ASA) score was obtained before surgery. Creatine kinase (CK), myocardium-specific creatine kinase (CK-MB) and troponin T (TnT) were analysed from venous blood, collected the day before surgery (−1) and postoperatively, within 24 hours (0) and on days one (+1) and four (+4). The overall three month mortality was 19.5%. Multivariate analyses showed that age, male sex and comorbidity (ASA) correlated with mortality (p=0.027, p=0.002, p<0.001, respectively). Surgery induced a two- to threefold increase of CK and CK-MB but without any correlation with mortality. However, high TnT levels >0.04 μg/l correlated significantly with death (days −1, +1 and +4, p=0.003, p=0.005 and p=0.003, respectively). Multivariate analyses, adjusted for age, sex and ASA category, confirmed this correlation (day +4, p=0.008). Thus, in elderly patients with comorbidities undergoing hip fracture surgery information on sex, age, ASA category and postoperative laboratory analyses on TnT provide the clinicians with useful information on patients at risk of fatal outcome.

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Introduction

Hip fracture is a moderate musculoskeletal trauma that mainly affects the older population with comorbid conditions. The number will increase markedly in coming years due to the ageing of the population [1]. Comorbidity and the double trauma may dispose them to serious postoperative adverse outcomes and a high mortality dominated by cardiovascular events [2–5]. Myocardial injury may be difficult to diagnose because of impaired communication, limitations of clinical manifestation and non-specific electrocardiographic (ECG) changes [6, 7]. The isoenzyme myocardium-specific creatine kinase (CK-MB) is expressed in the myocardium and CK in the skeletal muscle cells. These two enzymes have traditionally been analysed in plasma to distinguish myocardial injury and skeletal muscle injury [8, 9]. Troponins have been shown to be more specific and sensitive to cardiac injury [10, 11]. Increased plasma levels of troponin have also been reported in pulmonary

embolism, septicaemia and following major orthopaedic and cardiac surgery. In those conditions high plasma troponin levels have been associated with severe adverse outcomes and increased mortality [7, 12–15].

In this study we wanted to test the hypothesis that fatal outcome following hip fracture is not related to cardiomuscular plasma enzymes.

Materials and methods

The study was approved by the Regional Ethics Committee and National Medical Authorities and conducted in accordance with the Helsinki declaration.

A total of 302 consecutive patients over 75 years of age with dislocated hip fractures were enrolled in the study at Elverum (ECH) and Buskerud (BCH) central hospitals during the period 2005–2009. Comorbidity was routinely assessed according to the classification of the American Society of Anesthesiologists (ASA) [16]. All patients received loco-regional analgesia. A hemiprosthesis was inserted through a lateral incision and fixed with or without bone cement (Landos Titan or Landos Corail, DePuy, Warsaw, IN, USA).

Thromboprophylaxis (low molecular weight heparins) was administered routinely preoperatively (on hospital admission) with dalteparin 5000 IU s.c. (ECH) or enoxaparin 40 mgs.c. (BCH) and subsequently once daily for about one week.

Blood samples were obtained from an antecubital vein, collected preoperatively (−1) and postoperatively [within 24 hours (0)] and on days one [24–48 h (+1)] and four (+4). The blood samples were immediately processed and analysed according to local laboratory routines. Troponin T (TnT) and CK-MB were measured by electrochemiluminescence immunoassay (ELICA, Roche, Basel, Switzerland and Abbott, Abbott Park, IL, USA). CK was measured by absorption photometry (Roche, Basel, Switzerland and Abbott, Abbott Park, IL, USA). Values for TnT were only measured at the ECH study centre (n=146).

Descriptive statistics were mean and standard deviation if not otherwise stated. Differences between mortality groups were tested using a two-sample t test or chi-square test for continuous or categorical data, respectively. Non-parametric Mann-Whitney tests were done for TnT due to skewed distribution. A linear mixed model for repeated measurements with a random intercept and Bonferroni adjusted pairwise post hoc comparisons were used to analyse the biochemical markers with respect to mortality and repeated venous blood analyses. Univariate and stepwise multivariate logistic regression analyses were used to estimate unadjusted and adjusted odds ratios with respect to survival at the three month follow-up. Results from multivariate logistic regression were based on models including only significant terms from stepwise regression to maximise the number of patients included. Missing data were assumed to be completely at random. The significance level was set to $p<0.05$.

Results

Demographic and clinical characteristics of patients are shown in Table 1. There were 229 women and 72 men, with a mean age of 84.7 (SD 5.1) and 83.7 (SD 4.7) years, respectively. By three months, 59 of 302 (19.5%) had died, 62% women and 38% men.

ASA, male sex and age were significantly associated with mortality within three months (Table 1).

Within one day after surgery, the plasma levels of CK and CK-MB increased nearly threefold (inverse for the ratio). On days −1 and +1, CK and CK-MB values were significantly higher among those who died compared to those who survived (p=0.001 and p=0.031, respectively) (Fig. 1). On the fourth postoperative day, TnT plasma levels rose twofold in the mortality group and remained unchanged in the alive group. The plasma levels were significantly higher ($p<0.05$) in the mortality group at all sampling times except at day 0 (Fig. 1)

Table 1 Demographic and clinical characteristics of patients at 3-month follow-up

Characteristics	Alive (n=243)	Dead (n=59)	p values
Age, years (mean ± SD)	84.1 (5.1)	86.2 (4.6)	0.004
Sex			
Female	193 (79.4%)	37 (62.7%)	0.005
Male	50 (20.6%)	22 (37.3%)	
Mobility			
Not mobile	37 (15.8%)	10 (17.2%)	0.109
Living aid	23 (9.8%)	5 (8.6%)	
Crutches	51 (21.8%)	21 (36.2%)	
No aid	123 (52.6%)	22 (37.9%)	
ASA score			
I	10 (4.2%)	0 (0.0%)	<0.001
II	103 (42.9%)	9 (15.3%)	
III	116 (48.3%)	38 (64.4%)	
IV	11 (4.6%)	12 (20.3%)	

ASA American Society of Anesthesiologists

Minor deviations between total number of patients in categories compared to number alive or dead are due to missing data. Missing data are assumed to be completely at random

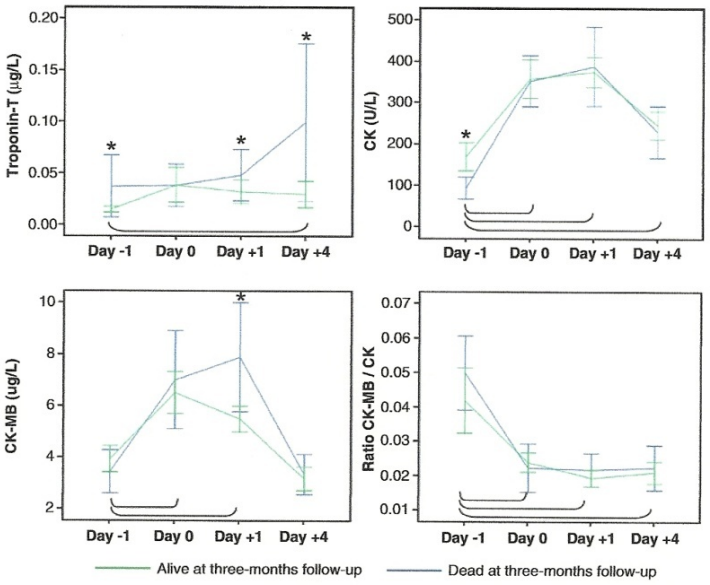

Fig. 1 Mean and 95% confidence intervals for troponin T, creatine kinase (CK), myocardium-specific creatine kinase (CK-MB) and ratio of CK-MB to CK before surgery, perioperatively and 1 and 4 days after surgery for 3-month mortality. Statistical significance ($p<0.05$) between mortality groups is indicated by an *asterisk*. Statistically significant ($p<0.05$) differences between before surgery and during follow-up are indicated by the *connecting lines*. *Day −1* 1 day before surgery, *day 0* within 24 h after the operation, *day +1* 24–48 h postoperatively, *day +4* 4 days after surgery

The TnT plasma concentrations were split into three equal-sized data subsets, i.e. ≤0.01, 0.01–0.04 and >0.04 µg/l, and the ratios of CK-MB to CK concentrations were split into two equal-sized data subsets, i.e. below and above 0.02. They were analysed for mortality association. Univariate logistic regression analyses showed that plasma concentrations above 0.04 µg/l before surgery correlated with three month mortality [odds ratio (OR) 10.9, 95% confidence interval (CI) 2.2–54.0, $p=0.003$] (Table 2). Stepwise multivariate logistic regression with age, sex, ASA category, levels of TnT and ratio of CK-MB to CK concentrations were performed. High TnT plasma concentration was associated with increased mortality (OR 6.1 95% CI 6–23.1, $p=0.008$) at day four after surgery. No statistically significant association was found for the ratio of CK-MB to CK during the entire sampling period when adjusted for age, sex and ASA (Table 3). Similar regression analyses were done for CK and CK-MB. On day +1, the CK-MB was associated with mortality (OR 1.1, 95% CI 1.02–1.2, $p=0.012$). We found that our hypothesis, stating no predictive value from cardio-muscular plasma enzymes with regard to early mortality in patients with hip fracture, was false.

Discussion

This prospective study on 302 elderly patients with hip fracture disclosed that 19.5% had died within three months. Preoperatively obtained basic patient information was shown to be of particular importance to assess the risk of postoperative mortality. ASA score on comorbidity, male sex and age correlated significantly with three month mortality, also described by other investigators [17–19].

Autopsy studies have shown that cardiovascular events are the main cause of death after hip fracture surgery [20, 21]. Autopsies are rarely done today and the direct cause of postoperative death has not been possible to establish in this or in other recently conducted studies.

In the elderly perioperative myocardial ischaemia is often clinically silent, without haemodynamic or notable ECG changes [22–25]. Over the years, biochemical plasma

Table 2 Results from univariate logistic regression models predicting 3-month mortality (death)

Variables		Unadjusted OR (95% CI)	*p* values
Age		1.1 (1.0–1.1)	0.004
If male		2.4 (1.3–4.4)	0.006
ASA		3.7 (2.2–6.1)	<0.001
If CK-MB/CK > 0.02			
Day −1		1.6 (0.8–3.4)	0.225
Day 0		0.7 (0.3–1.6)	0.413
Day +1		1.5 (0.8–2.9)	0.239
Day +4		1.2 (0.6–2.4)	0.620
TnT			
Day −1	≤0.01	1.0 (reference)	
	0.01–0.04	1.5 (0.4–6.0)	0.532
	>0.04	11.0 (2.2–54.6)	0.003
	≤0.01	1.0 (reference)	
Day 0	0.01–0.04	1.5 (0.4–5.4)	0.556
	>0.04	2.9 (0.7–11.0)	0.127
	≤0.01	1.0 (reference)	
Day +1	0.01–0.04	1.6 (0.4–7.4)	0.512
	>0.04	6.0 (1.7–21.1)	0.005
	≤0.01	1.0 (reference)	
Day +4	0.01–0.04	3.3 (0.7–15.0)	0.126
	>0.04	7.0 (1.9–25.6)	0.003

OR odds ratio, *CI* confidence interval, *ASA* American Society of Anesthesiologists, *CK-MB/CK* ratio of myocardium-specific creatine kinase to creatine kinase, *day −1* 1 day before surgery, *day 0* within 24 h after surgery, *day +1*24–48 h postoperatively, *day +4* 4 days after surgery

markers have been used to distinguish myocardial injury from skeletal muscle damage, an approach also adopted in this study. CK, reflecting the general skeletal muscle trauma, increased perioperatively. This finding is in line with a recent study in elective hip replacement surgery [26]. Potential heart muscle damage was investigated in this study with CK-MB and TnT analyses. We found small and inconsistent differences for CK and CK-MB plasma levels between those who died and those who survived. The ratio of CK-MB to CK was decreased from hospital admission (day −1) to day 0 and stabilised, indicating that skeletal muscle damage dominated and that any myocardial injury remained undetected. Logistic regression analyses showed no correlation with postoperative mortality. This analysis suggests that CK and CK-MB are unspecific enzymes that are not distinct for skeletal and cardiac muscle damage following a hip fracture and are not feasible as prognostic markers of mortality, a finding consistent with other investigators [27].

Release of troponins into the circulation is considered to specifically reflect cardiac injury [28]. In our study we analysed TnT and found that the plasma concentration was significantly higher on the fourth postoperative day in patients that subsequently died compared to those who were alive. Patients with TnT levels above 0.04 μg/l had a six times higher risk of dying vs those with normal plasma levels. This calculation was robust when correction was done for age, sex and comorbidity (ASA score). These results fit with other reports that showed a second wave of troponin elevation several days after surgery which correlated with postoperative mortality [13, 29].

In summary, this study showed that basic clinical information on sex, age and comorbidity (ASA score) and a high postoperative plasma concentration of TnT >0.04 μg/l are robust predictors of three month postoperative mortality in the elderly undergoing hip fracture surgery. This information may be of importance for therapeutic and post-hospital health care intervention.

Table 3 Results from multivariate stepwise logistic regression models predicting 3-month mortality (death)

Variables	Day −1		Day 0		Day +1		Day +4	
	Adjusted OR (95% CI)	*p* values	Adjusted OR (95% CI)	*p* values	Adjusted OR (95% CI)	*p* values	Adjusted OR (95% CI)	*p* values
Age	1.1 (1.0–1.2)	0.006	1.1 (1.0–1.2)	0.006	1.1 (1.0–1.2)	0.001	1.1 (1.0–1.2)	0.027
If male	2.4 (1.2–4.6)	0.013	2.4 (1.2–4.6	0.013	2.7 (1.4–5.1)	0.002	–	
ASA	3.3 (2.0–5.6)	<0.001	3.3 (2.0–5.6)	<0.001	–		–	
CK-MB/CK	–		–		–		–	
TnT								
≤ 0.01	–		–		–		1.0 (reference)	–
0.01–0.04	–		–		–		1.9 (0.4–9.4)	0.450
>0.04	–		–		–		6.1 (1.6–23.1)	0.008

OR odds ratio, *CI* confidence interval, *ASA* American Society of Anesthesiologists, *CK-MB/CK* ratio of myocardium-specific creatine kinase to creatine kinase, *day −1* 1 day before surgery, *day 0* within 24 h after surgery, *day +1*24–48 h postoperatively, *day +4* 4 days after surgery

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ASA	3.3 (2.0–5.6)	<0.001	3.3 (2.0–5.6)	<0.001	–		–	
CK-MB/CK	–		–		–		–	
TnT								
≤ 0.01	–		–		–		1.0 (reference)	–
0.01–0.04	–		–		–		1.9 (0.4–9.4)	0.450
>0.04	–		–		–		6.1 (1.6–23.1)	0.008

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Conflict of interest The authors declare that they have no conflict of interest.

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