

Delirium in elderly patients: pathophysiological mechanisms and clonidine treatment

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Abbreviations

ADL	Activities of Daily Living
APACHE II	Acute Physiology and Chronic Health Evaluation II
ASA score	American Society of Anesthesiologists score
BID	Twice daily (bis in die)
BEN	Bjørn Erik Neerland
BP	Blood Pressure
BPM	Beats Per Minute
CAM	Confusion Assessment Method
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CDR	Clinical Dementia Rating scale
CERAD	The Consortium Establish a Registry for Alzheimer's Disease
CIRS	Cumulative Illness Rating Scale
Cmax	Maximum plasma concentration
CNS	Central Nervous System
Cnull	Median trough concentration
CRP	C-reactive protein
CSF	Cerebrospinal Fluid
DRS-R-98	Delirium Rating Scale Revised-98
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 th edition
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HPA	Hypothalamic - Pituitary - Adrenaline
HR	Heart Rate
HUT	Head-up tilt-test
ICD-10	International Classification of Diseases, 10 th edition
ICU	Intensive Care Unit
IL	Interleukin
IMP	Investigational Medicinal Product
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
KRH	Karen Roksund Hov
LUCID	The Oslo Study of Clonidine in Elderly Patients with Delirium
MAP	Mean Arterial Pressure
MDAS	Memorial Delirium Assessment Scale
MMSE	Mini Mental State Examination
NYHA	New York Heart Association
OSLA	Observational Scale of Level of Arousal
RASS	Richmond Agitation Sedation Scale
RCT	Randomised Controlled Trial
REK	Regional Committee for Ethics in Medical Research in Norway
SQID	Single Question In Delirium

List of publications

I: Associations between Delirium and Preoperative Cerebrospinal Fluid C-Reactive Protein, Interleukin-6, and Interleukin-6 Receptor in Individuals with Acute Hip Fracture

Neerland BE, Hall RJ, Seljeflot I, Frihagen F, MacLulich AM, Raeder J, Wyller TB, Watne, LO. Journal of the American Geriatrics Society. 2016;64(7):1456-63.

II: Perioperative Hemodynamics and Risk for Delirium and New Onset Dementia in Hip Fracture Patients; a Prospective Follow-up Study

Neerland BE, Krogseth M, Juliebø V, Ranhoff AH, Engedal K, Frihagen F, Ræder J, Wyller TB, Watne LO. Manuscript.

III: Autonomic cardiovascular control in elderly patients with acute infection and delirium: a pilot study of orthostatic stress responses

Neerland BE, Wyller TB, Wyller VB. Manuscript.

IV: The protocol of the Oslo Study of Clonidine in Elderly Patients with Delirium; LUCID: a randomised placebo-controlled trial

Neerland BE*, Hov KR*, Wyller VB, Qvigstad E, Skovlund E, MacLulich AM, Wyller TB. BMC Geriatrics. 2015;15(1):7.

V: The use of clonidine in elderly patients with delirium: pharmacokinetics and hemodynamic responses

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1 Summary

1.1 Summary in English

Background

Delirium is often also called “acute confusional state” and is characterized by an acute decline in attention and cognition. Delirium is common, and as many as 20% of older patients in hospital suffer from it. The condition is associated with increased risk of in-hospital complications, suffering and distress for patients and their relatives, and with bad outcomes.

The pathophysiology of delirium remains poorly understood. Leading hypotheses focus on neurotransmission, inflammation and acute stress as possible mechanisms. Alterations in the autonomic nervous system (ANS) activity might also be involved. We wanted to examine whether delirium is associated with high C-reactive protein (CRP), interleukin-6 (IL-6), and soluble IL-6 receptor (sIL-6R) levels in the cerebrospinal fluid (CSF). We also aimed at exploring autonomic cardiovascular control in geriatric patients with and without delirium.

Delirium is common in hip fracture patients and many risk factors have been identified. Controversy exists regarding the possible impact of intraoperative control of blood pressure upon acute (delirium) and long term (dementia) cognitive decline. We wanted to study possible associations between perioperative hemodynamic changes, use of vasopressor drugs, risk of delirium and risk of new-onset dementia.

The base of all prevention and treatment of delirium is a multicomponent and non-pharmacological intervention. There are no approved drugs for the treatment of delirium. Drug trials in delirium are heterogeneous, and there are only a few placebo controlled, randomised trials studying older medical patients with delirium.

We wanted to design and initiate a randomised placebo controlled trial (RCT) investigating treatment of delirium in medical patients with the alpha-2 adrenoceptor agonist clonidine; to investigate the plasma concentrations and hemodynamic effects of clonidine, and to evaluate the dosage regime. This thesis describes in detail how the The Oslo Study of Clonidine in Elderly Patients with Delirium (LUCID) was planned, its design, methods, and the screening process leading to the inclusion of the first 20 participants.

Methods

In previous studies of delirium in hip fracture patients in Oslo and Edinburgh, serum was collected preoperatively and CSF just before the onset of spinal anesthesia. These samples have been analysed in order to explore possible pathogenic mechanisms in delirium. Cytokine levels in serum and CSF samples were determined using an enzyme-linked immunosorbent assay. Some of the patients included in Oslo were assessed with cognitive tests 6 or 12 months after the fracture. We used these data to explore the effect of perioperative variables on delirium and new-onset dementia.

The patients were assessed for delirium pre- and postoperatively. Pre-fracture cognitive function was assessed using the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE) and by consensus diagnosis. The presence of new-onset dementia was determined at follow-up evaluation at six or twelve months after surgery. Blood pressure was recorded at admission, perioperatively and postoperatively.

A head-up tilt test (HUT) was performed in patients acutely admitted to the geriatric ward with an infection, to explore autonomic cardiovascular control in patients with and without delirium, and particularly to assess possible differences in heart rate variability according to delirium status. Continuous, non-invasive hemodynamic variables were obtained during supine rest (5 minutes) and head-up tilt (HUT) to 15 degrees (10 minutes). Heart rate (HR), blood pressures (BP) and stroke volume (SV) were recorded beat-to-beat. Cardiac output (CO), total peripheral resistance (TPR), end-diastolic volume (EDV) and heart rate variability (HRV) values were calculated.

LUCID is investigating the use of clonidine in medical patients > 65 years with delirium and was designed as a randomised, placebo-controlled, double-blinded, parallel group study with 4-month prospective follow-up. Patients were randomised to orally administered clonidine or placebo until delirium free or no subsyndromal delirium for 2 days, or after a maximum of 7 days treatment. The treatment group was given a loading dose (75 µg every 3rd hour up to a maximum of 4 doses) to reach steady state and further 75 µg twice daily until delirium free for 2 days, discharge or a maximum of 7 days of treatment. Blood pressure (BP) and heart rate (HR) were monitored just before every dose. Plasma concentrations of clonidine were measured. Our pre-specified plasma concentration target range was 0.3-0.7 µg/L.

Results

In patients without prior cognitive impairment, CSF CRP levels were higher in participants with delirium (median 0.05 µg/mL, interquartile range (IQR) 0.02–0.12 µg/mL) than in those without delirium (median 0.01 µg/mL, IQR 0.00–0.06 µg/mL) ($P = .01$); there were no differences in participants with prior cognitive impairment.

Preoperative delirium was present in 149 of 536 (28%) assessable hip fracture patients, and 124 of 387 (32%) developed delirium postoperatively (incident delirium). The following risk factors for incident delirium in patients without pre-fracture cognitive impairment were identified: low body mass index, low level of functioning, severity of physical illness, and receipt of ≥ 2 blood transfusions. New-onset dementia was diagnosed at follow-up in 26 of 213 (12%) patients, associated with severity of physical illness, delirium, receipt of vasopressor drugs perioperatively and high mean arterial pressure postoperatively.

HR, BP, SV, CO, TPR and EDV were similar across the two groups of geriatric patients with infection at rest, but there was a trend towards stronger increase in systolic BP and HR during HUT in the delirium group. At rest, all HRV indices were higher in the delirium group, but not statistically significant. During HUT, the delirium group had higher PSD (representing total variability) ($p=0.06$) and a lower LF/HF-ratio (an index of sympathovagal balance) than the control group ($p=0.06$). Also, delirious patients had a significantly stronger reduction in SDNN (representing total variability) from baseline than the controls ($p= 0.01$) during HUT.

More than four thousand patients were screened for participation in LUCID, but only 20 patients were included in almost 3 years. 3 hours after the first dose of 75µg clonidine, plasma concentration levels rose to median 0.35 (range 0.24-0.40) µg/L and median trough concentration (C₀) at day 2 was 0.70 (0.47-0.96) µg/L. At steady state, median C₀ was 0.47 (0.36-0.76) µg/L, rising to a level of 0.74 (0.56-0.95) µg/L (C_{max}) three hours post dose. In the clonidine group, there was a drop in systolic BP (SBP) from baseline median 141 (range 124-190) mmHg to 3 hours after the 4th loading dose (128 (98-153) mmHg) $p= 0.04$, and from baseline to day 2 (135 (81-170) mmHg), $p=0.06$.

Conclusions

High CSF levels of CRP may be associated with delirium. Different pathophysiological mechanisms may operate in different subgroups, notably in relation to the presence of prior cognitive impairment.

Risk factors for incident delirium seem to differ according to pre-fracture cognitive status. The use of vasopressors during surgery and/or postoperative hypertension might possibly be related to new-onset dementia after hip fracture.

Our results indicate that patients with delirium have altered ANS activity. Due to a limited sample size, this should be further investigated in larger groups.

The plasma concentration of clonidine was mainly within the expected therapeutic range, but in the higher end, especially at trough concentration at day 2. The hemodynamic changes during clonidine treatment were as expected with trends towards lower blood pressure and heart rate in patients treated with clonidine, but with dose adjustments based on SBP this protocol seems safe.

There seems to be a theoretically good rationale to expect a beneficial effect of clonidine in patients with delirium. We have presented a feasible dosage regimen. To reach a large enough sample size, and due to strict exclusion criteria and safety issues, clonidine would probably be better explored in a less frail population.

1.2 Norsk sammendrag

Bakgrunn

Delirium kalles også ofte "akutt forvirring" og kjennetegnes av en akutt forverring av oppmerksomhetsfunksjoner og kognitiv funksjon. Tilstanden er vanlig, og så mange som 20 % av eldre pasienter på sykehus får delirium. Delirium er forbundet med økt risiko for komplikasjoner under sykehusoppholdet, og oppleves belastende for både pasientene og deres pårørende. Tilstanden er også forbundet med dårlig prognose. Vi vet lite om hva som skjer i hjernen ved delirium og det er lite kunnskap om effektive medikamentelle behandlingsmuligheter.

Ulike patofysiologiske hypoteser er foreslått, blant annet endret nevrotransmisjon, betennelse og akutte stressresponser. Endret aktivitet i det autonome nervesystemet (ANS) kan også være involvert. Vi ønsket å undersøke om delirium er forbundet med høye nivåer av C-reaktivt protein (CRP), interleukin-6 (IL-6) og av løselig IL-6-reseptor (sIL-6R) i spinalvæsken (CSF). Et formål var også å undersøke autonom kardiovaskulær kontroll hos geriatriske pasienter med og uten delirium.

Delirium er svært vanlig hos hoftebruddspasienter, og mange risikofaktorer er identifisert. Det er noe usikkerhet rundt sammenhenger mellom perioperativ blodtrykkskontroll og akutt (delirium) og vedvarende (demens) kognitiv svikt. Vi ønsket å studere mulige sammenhenger mellom perioperative hemodynamiske forandringer, bruk av vasopressor, risiko for delirium etter operasjonen og risiko for å utvikle demens.

Det viktigste i forebygging og behandling av delirium er ikke-farmakologiske tiltak. Det finnes ingen godkjente legemidler for behandling av delirium. Design i tidligere medikamentstudier har variert og bare et fåtall av studiene har vært placebokontrollerte.

Vi ønsket å designe og å igangsette en randomisert, placebokontrollert studie (RCT) som undersøkte behandling med alfa-2 adrenoceptoragonisten klonidin hos medisinske pasienter med delirium. Vi ville også måle plasmakonsentrasjonene av klonidin og analysere de hemodynamiske effektene av

behandlingen, med tanke på å evaluere doseringsregimet. Denne avhandlingen gir en detaljert beskrivelse av hvordan medikamentstudien LUCID ble planlagt. Det gis en beskrivelse av design og metoder som ble benyttet, samt en oppsummering av screeningen og inkluderingen av de første 20 deltakerne.

Metode

Vår forskergruppe har studert hoftebruddspasienter tidligere, og blant annet samlet spinalvæske og blodprøver i forbindelse med operasjonen. Disse prøvene er analysert for å lære mer om mulige sammenhenger ved delirium. I noen av analysene har vi også inkludert prøver som ble samlet inn i Edinburgh. Noen av pasientene som deltok i Oslo ble vurdert med kognitive tester 6 eller 12 måneder etter hoftebruddet. Vi har brukt disse dataene til å undersøke mulige sammenhenger mellom forhold rundt selve operasjonen og utvikling av delirium, og med utvikling av demens ved oppfølging.

Pasientene ble vurdert for delirium pre- og postoperativt. Kognitiv funksjon før hoftebruddet ble vurdert ved hjelp av spørreskjemaet Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE) og ved konsensusdiagnose. Kognitiv funksjon og oppfylging av kriterier for en eventuell demensdiagnose ble vurdert ved oppfølging seks eller tolv måneder etter operasjonen. Blodtrykk ble registrert ved innleggelse, perioperativt og postoperativt.

Vi gjorde en vipptest (HUT) hos pasienter akutt innlagt i geriatrik avdeling med en infeksjon, for å undersøke autonom kardiovaskulær kontroll hos pasienter med og uten delirium. Spesielt ønsket vi å vurdere mulige forskjeller i hjerterefrekvensvariabilitet i henhold til deliriumstatus. Kontinuerlige, ikke-invasive hemodynamiske variabler ble registrert mens pasienten lå flatt i sengen (5 minutter) og ved vipping (HUT) til 15 grader (10 minutter). Hjerterefrekvens (HR), blodtrykk (BP) og slagvolum (SV) ble registrert kontinuerlig. Minuttvolum (CO), total perifer motstand (TPR), endediastolisk volum (EDV) og hjerterefrekvensvariabilitet (HRV) ble beregnet.

I LUCID undersøker vi effekten av behandling med klonidin hos medisinske pasienter > 65 år med delirium. Studien er en randomisert, placebokontrollert, dobbeltblindet, parallellgruppe studie med 4 måneders prospektiv oppfølging. Pasienter ble randomisert til oralt administrert klonidin eller placebo. Behandlingen varte til de hadde vært fri for symptomer på delirium eller subsyndromalt delirium i 2 dager, eller i maksimalt 7 dager. Behandlingsgruppen ble gitt en opptrappingsdose (75 µg hver tredje time opp til maksimalt 4 doser) for å oppnå steady state og deretter 75 µg to ganger daglig. Blodtrykk og puls ble målt like før hver dose. Plasmakonsentrasjoner av klonidin ble målt. Vi ønsket å oppnå en plasmakonsentrasjon på 0,3-0,7 µg / L.

Resultater

Hos hoftebruddspasienter uten kognitiv svikt før bruddet, var CRP-nivåene i spinalvæsken høyere hos pasienter med delirium (median 0,05 µg / ml, interkvartilområde (IQR) 0,02-0,12 µg / mL) enn hos de uten delirium (median 0,01 µg / mL, IQR 0,00-0,06 µg / mL) = 0.01). Det var ikke forskjeller mellom pasienter med tidligere kognitiv svekkelse.

Preoperativt delirium ble diagnostisert hos 149 av 536 (28 %) hoftebruddspasienter, og 124 av 387 (32 %) utviklet delirium etter operasjonen. Vi identifiserte følgende risikofaktorer for postoperativt delirium hos pasienter uten kognitiv svikt før bruddet: lav kroppsmasseindeks, lavt funksjonsnivå, alvorlighetsgrad av fysisk sykdom og ≥ 2 blodoverføringer. 26 av 213 (12 %) pasienter ble vurdert til å ha nyoppstått demens ved oppfølging. Dette var assosiert med alvorlighetsgrad av fysisk sykdom, delirium, behandling med vasopressor perioperativt og høyt blodtrykk postoperativt.

I hvile var de ordinære hemodynamiske variablene (puls, blodtrykk, total perifer motstand, minuttvolum, etc) like i de to gruppene av geriatrike pasienter med infeksjon. Det var imidlertid en trend til større økning i systolisk blodtrykk og puls under vippetesten i deliriumgruppen. I hvile var alle HRV-indeksene høyere i deliriumgruppen, men ikke statistisk signifikant. Under vipping hadde deliriumgruppen høyere PSD (representerer totalvariabilitet) ($p = 0,06$) og en lavere LF / HF-ratio (et uttrykk for sympatikovagal balanse) enn kontrollgruppen ($p = 0,06$). Dessuten hadde pasienter med delirium en signifikant sterkere reduksjon i SDNN (som representerer total variabilitet) fra baseline enn kontrollene ($p = 0,01$) under vipping.

Mer enn fire tusen pasienter ble screenet for deltakelse i LUCID, men bare 20 pasienter var inkludert i løpet av nesten 3 år. Plasmakonsentrasjonsnivåene steg til median 0,35 (0,24-0,40) $\mu\text{g} / \text{L}$ 3 timer etter den første dosen med 75 μg klonidin. Median konsentrasjon (C_0) på dag 2 var 0,70 (0,47-0,96) $\mu\text{g} / \text{L}$. Ved steady state var median C_0 0,47 (0,36-0,76) $\mu\text{g} / \text{L}$, og økte til 0,74 (0,56-0,95) $\mu\text{g} / \text{L}$ (C_{max}) tre timer etter inntak. I klonidiningruppen falt systolisk blodtrykk fra utgangspunktet på median 141 (124-190) mmHg til 3 timer etter den fjerde opptrappingsdosen (128 (98-153) mmHg) $p = 0,04$ og fra utgangspunktet til dag 2 (135 (81-170) mmHg), $p = 0,06$.

Konklusjon

Høye nivåer av CRP i spinalvæske kan være assosiert med delirium. Ulike patofysiologiske mekanismer kan gjøre seg gjeldende i ulike pasientgrupper, spesielt med tanke på kognitiv status før bruddet. Risikofaktorer for postoperativt delirium hos hoftebruddspasienter synes også å være forskjellige, avhengig av kognitiv status før bruddet.

Bruk av vasopressorer under operasjon og / eller postoperativ hypertensjon kan muligens være assosiert med nydiagnostisert demens ved oppfølging etter 6 eller 12 måneder etter hoftebruddet.

Resultatene fra vippetestene indikerer at pasienter med delirium har en endret autonom aktivitet. Studien var liten og hypotesegenererende, og man trenger større studier for å kunne si noe konklusivt.

Plasmakonsentrasjonen av klonidin var hovedsakelig innenfor det forventede terapeutiske området, men det øvre sjiktet, særlig dag 2. De hemodynamiske endringene under klonidinbehandlingen var også som forventet, med tendenser til lavere blodtrykk og puls i behandlingsgruppen. Det synes fortsatt å være en rimelig god grunn til å forvente gunstig effekt av klonidin hos pasienter med delirium. Vi har utarbeidet et gjennomførbart og trygt behandlingsopplegg, men har foreslått dosejusteringer basert på målinger av puls og blodtrykk. På grunn av strenge eksklusjonskriterier og mange potensielle bivirkninger av klonidin hos akutt syke geriatrike pasienter ble få pasienter inkludert i løpet av tre år. Videre studier av effekten av klonidin på delirium bør kanskje heller inkludere mindre skrøpelige pasienter.

“WHEN IN CONTINUED FEVERS OCCUR DIFFICULTY OF BREATHING AND DELIRIUM, IT IS A
FATAL SIGN”

APHORISMS, IV,L

“IN ACUTE FEVERS (...); IF THEY (THE ARMS) MOVE BEFORE THE FACE, HUNT IN THE
EMPTY AIR, PLUCK NAP FROM THE BEDCLOTHES, PICK UP BITS, AND SNATCH CHAFF FROM
THE WALLS - ALL THESE SIGNS ARE BAD, IN FACT DEADLY”

PROGNOSTIC, IV

Hippocrates, 460-370 BC

2 Introduction

Hippocrates' statements are more than two thousand years old - are they still true and relevant? Is delirium during the course of acute illness a fatal sign? What is delirium and how should it be diagnosed (moving arms and pluck nap from the bedclothes)? In which way is delirium "bad" - and can we do something about it?

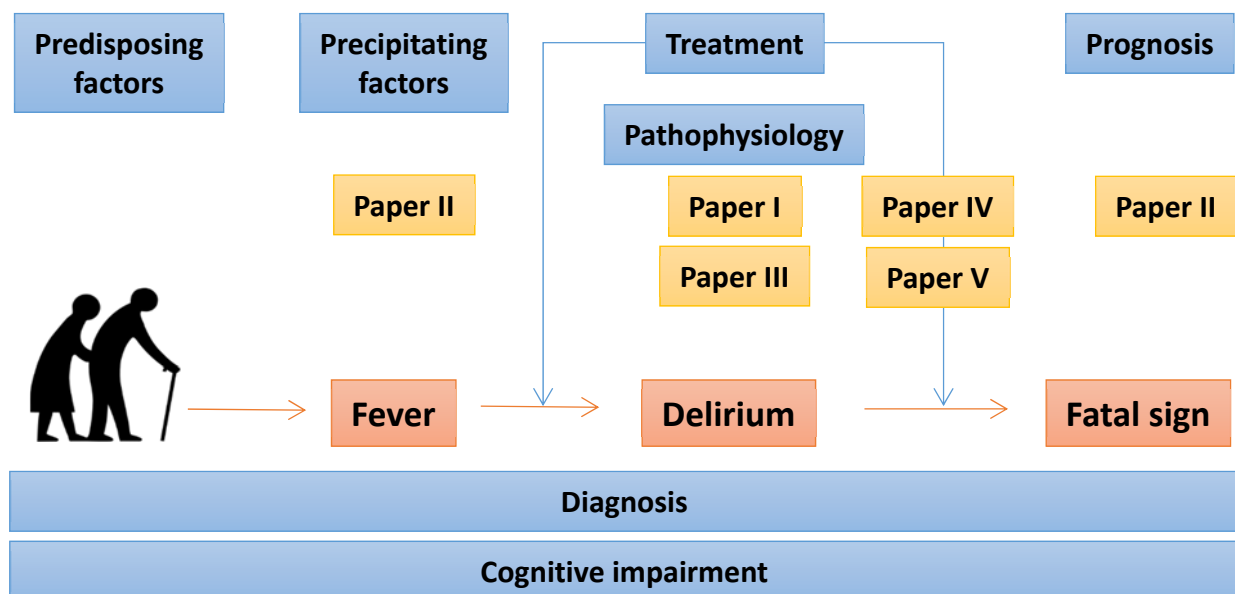
Delirium is common, and as many as 20% of older patients in hospital suffer from delirium. It is undetected in about half the cases, and associated with increased risk of in-hospital complications, suffering and distress for patients and their relatives, and with bad outcomes such as chronic cognitive impairment. However, still little is known about the underlying pathophysiology and pharmacological treatment options.

This thesis does not aim to answer all the questions raised by Hippocrates' quotes, but his observations are still relevant in delirium research today. Ongoing discussions regarding diagnosis affect all delirium studies. The relationship between acute delirium and chronic cognitive impairment and dementia is indeed a "hot topic" and more knowledge is needed.

The five papers included in this thesis hopefully contribute to different parts of the delirium research field (figure 1): Precipitating factors for delirium in hip-fracture patients and variables associated with bad prognosis (dementia); pathophysiological aspects with focus on neuroinflammation, autonomic nervous activity and hemodynamic variables; and the possible treatment of delirium with clonidine.

Figure 1. The papers in this thesis and their relationship to some delirium research topics

The red boxes refer to Hippocrates: "When in continued fevers occur difficulty of breathing and delirium, it is a fatal sign" (*Aphorisms, IV,L*)



This thesis describes in detail how the The Oslo Study of Clonidine in Elderly Patients with Delirium (LUCID) was planned, its design, methods, and the screening process leading to the inclusion of the first 20 participants. LUCID aimed at studying any beneficial effect of clonidine on delirium in geriatric patients. The first part of the trial included a study of the pharmacokinetics and hemodynamic effects of clonidine in this population. The thesis will *not* present the results of primary or secondary outcomes from the RCT (effects on delirium), but the pharmacological aspects will be included.

This thesis is not primarily about chronic cognitive impairment or dementia, but because one of the papers (paper II) has new-onset dementia as one of the outcomes, I have briefly mentioned dementia in the introduction. However, pathophysiological mechanisms and different diagnostic criteria for dementia are not discussed.

3 Background

3.1 Delirium

In this section I present some basic facts about delirium, as a background for the thesis. More thorough discussions of delirium pathophysiology and pharmacological delirium treatment, both main topics in my dissertation, are provided in section 3.3 and 3.4, respectively.

3.1.1 Definition, diagnosis and clinical features

Delirium is often also called “acute confusional state” or “acute brain failure” and is characterized by an acute decline in attention and cognition (Inouye et al., 2014). There is no recognized physiological measure (no laboratory test or imaging sign) of delirium, and the diagnosis is made clinically.

Different diagnostic criteria for delirium have been developed, and the most common used in research are the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (AmericanPsychiatricAssociation, 2000), 5th edition (DSM-5) (AmericanPsychiatricAssociation, 2013) and International Classification of Diseases, 10th edition (ICD-10) (WorldHealthOrganization, 2008) criteria (Table 1 to 3). In the studies included in this thesis, delirium has been diagnosed according to the DSM-IV and the DSM-5 criteria. The DSM-5 criteria were published in 2013.

The DSM-5 criteria states that delirium is characterized by an acute disturbance in attention and awareness. The disturbance has a tendency to fluctuate during the day and represents a change from baseline attention and awareness. In addition, cognitive symptoms such as memory impairment, disorientation, delusions and/or hallucinations are present. By definition, the mental disturbance is caused by a medical condition, substance intoxication or withdrawal, or is due to multiple etiologies.

The concept of delirium in the different criteria overlaps considerably, but there are some differences (Meagher et al., 2014b, Adamis et al., 2015b). Some of the most important are:

- In DSM-5 the term ‘consciousness’ used in DSM-IV is replaced by “awareness and attention”.
- DSM-5 emphasises that the cognitive disturbances seen in delirium cannot better be “explained by a pre-existing, established or evolving neurocognitive disorder” (in most cases this is dementia). It specifically excludes coma from being labelled as delirium. However, if reduced arousal (but not as severe as in coma) impairs the ability to engage with cognitive testing, it is deemed as severe inattention (EDA/ADS 2014).
- Only the ICD-10 includes psychomotor disturbances and sleep disturbance in delirium, but the criteria do not explicitly discriminate delirium from other pre-existing neurocognitive disorders.

Neither of the diagnostic criteria provides information on what specific tests should be used in the assessment of attention, arousal or cognition. Neither do they address how to assess pre-existing cognitive impairment, like dementia (Morandi et al., 2017). Inattention is a core feature in delirium, but attention has multiple domains (Morandi et al., 2017), and it is not clear in the diagnostic criteria which domain should be tested and how. This is an important challenge, as attention might be impaired also in dementia. These are practical limitations for both researchers and clinicians, and have been addressed the last years (Morandi et al., 2017). We have been increasingly attentive to these diagnostic challenges during our work.

The term *subsyndromal* delirium is not very well defined (Cole et al., 2013). It has been argued that considering delirium as a binary phenomenon is an oversimplification. Delirium is more likely to be described as a continuum (Radtke et al., 2010). The term subsyndromal delirium has been introduced

to describe a clinical condition that falls on a continuum between no symptoms and delirium defined by the DSM-5 criteria. Subsyndromal delirium is associated with poor outcomes (Cole et al., 2013, Shim et al., 2015). There is no standardized definition of subsyndromal delirium, but it is argued that inattention should be central to its definitions (Meagher et al., 2014a). For our study (LUCID), we used the following definition (Paper IV):

Subsyndromal delirium is defined as evidence of change, in addition to any one of these: (a) altered arousal, (b) attentional deficits, (c) other cognitive change, (d) delusions or hallucinations. DSM-5 criteria D and E must be met.

Table 1. DSM-IV-TR Criteria for Delirium
A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

Table 2. DSM-5 Criteria for Delirium
A. A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).
D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
E. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiologies

Table 3. ICD-10 Criteria for Delirium (Delirium, not induced by alcohol and other psychoactive substances)
A. Clouding of consciousness, that is, reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention.
B. Disturbance of cognition, manifest by both: (1) impairment of immediate recall and recent memory, with relatively intact remote memory (2) disorientation in time, place, or person
C. At least one of the following psychomotor disturbances: (1) rapid unpredictable shifts from hypoactivity to hyperactivity (2) increased reaction time (3) increased or decreased flow of speech (4) enhanced startle reaction
D. Disturbance of sleep or the sleep/wake cycle, manifest by at least one of the following: (1) insomnia, which in severe cases may involve total sleep loss, with or without daytime drowsiness, or reversal of the sleep/wake cycle (2) nocturnal worsening of symptoms (3) disturbing dreams and nightmares that may continue as hallucinations or illusions after awakening
E. Rapid onset and fluctuations of the symptoms over the course of the day.
F. Objective evidence from history, physical and neurological examination, or laboratory tests of an underlying cerebral or systemic disease (other than psychoactive substance-related) that can be presumed to be responsible for the clinical manifestations in A to D.

3.1.2 Epidemiology

Delirium is highly prevalent in acute care hospitals, with the highest rates noted in elderly patients and in severely ill patients in postoperative and intensive care settings (Vasilevskis et al., 2012, Inouye et al., 2014). The prevalence among hip-fracture patients is about 50% (Bruce et al., 2007), and in mechanically ventilated ICU-patients as many as 2/3 patients are reported to have delirium (Pandharipande et al., 2013).

In a point prevalence study from an acute general hospital in Ireland, delirium was diagnosed in 19.6% of the inpatients on 15th of May 2010 (Ryan et al., 2013). The prevalence was highest in the geriatric population and among surgical patients. However, delirium was found across all hospital departments. The prevalence of 20% in the Irish study was confirmed also in a study of age-specific rates of delirium in acute general medicine (Pendlebury et al., 2015). Delirium affected 20 % of all acute medical admissions. The risk increased with age from 3% having delirium at <65 years to 36% at 75 years or higher. Delirium was associated with increased mortality, longer hospital stay, an increased risk of falling and increased dependency among survivors.

3.1.3 Risk factors and precipitating factors

The aetiology of delirium is considered to be multifactorial, and can be seen as an interrelationship between predisposing and precipitating factors (Inouye and Charpentier, 1996). In vulnerable patients, such as those with pre-existing cognitive impairment, high age and multimorbidity, a seemingly benign precipitating insult might be enough to induce delirium. In more fit, younger patients, delirium will develop only after exposure of a more noxious insult such as major surgery or mechanical ventilation in the ICU.

Older age, cognitive impairment/dementia, a history of delirium, functional impairment and impaired vision and/or hearing are universally acknowledged risk factors for delirium (Inouye et al., 2014, Bruce et al., 2007, Ahmed et al., 2014, Fong et al., 2015, Bitsch et al., 2006). A low body mass index (BMI), low albumin, as well as multiple comorbidities and polypharmacy are also consistently reported risk factors (Oh et al., 2015, Inouye et al., 2014).

The most commonly reported precipitating factors are psychoactive drugs, use of physical restraints or bladder catheter, as well as metabolic and physiological abnormalities, infections or major surgery (Inouye et al., 2014).

3.1.4 Cognitive trajectories and prognosis

Delirium is associated with several unfavourable outcomes in different settings, as falls and other in-hospital complications, increased length of hospital stay, functional and cognitive decline, and need for institutionalization (Marcantonio et al., 2001, Witlox et al., 2010, Gross et al., 2012, Dasgupta and Brymer, 2013).

In critical care, associations have been found between delirium and ICU length of stay, hospital length of stay, and days of mechanical ventilation. Further, emerging data exist on persistence of cognitive impairment after critical illness, and that the duration of delirium in the ICU is independently associated with cognitive function at 3 and 12 months (Pandharipande et al., 2013, Girard et al., 2010a).

There are important relationships between delirium and dementia (Fong et al., 2017, Fong et al., 2015). Both conditions are common in elderly patients, either as separate conditions or present both at the same time (delirium superimposed upon dementia). This has some very important implications, both clinically and when it comes to pathophysiology and biomarker studies. The interface between dementia and delirium has been highlighted the last years.

1. Dementia is a well-established risk factor for delirium (Ahmed et al., 2014, Fong et al., 2015).

Cognitive impairment makes a person vulnerable to develop delirium in the presence of a precipitating event. In patients with severe dementia, the precipitating cause can be quite “minor”, like a mild infection or a sedating drug. In patients with a previous diagnosis of dementia, 60-80% develops delirium when acutely admitted to hospital (Gross et al., 2012).

2. The later years, increasing evidence has emerged that delirium in the presence of an existing dementia accelerates the cognitive decline (Fong et al., 2009, Davis et al., 2012, Davis et al., 2017). This could be just an acceleration of the underlying dementia pathology, but there is some support that the cognitive decline seen after a delirium episode is not simply due to dementia pathology, but

could be an interaction between delirium and dementia, with a synergistic effect on the speed of cognitive decline (Davis et al., 2017).

3. There is also increasing evidence that delirium per se may increase the risk of dementia. Potential mechanisms are, however, still unresolved. At least three different mechanisms are possible (Fong et al., 2015): 1. Delirium is unmasking an already underlying and undiagnosed/preclinical dementia. The underlying dementia pathology is responsible for the cognitive decline seen after the delirium episode. 2. It is the precipitating cause of delirium that contributes both to delirium and the subsequent cognitive decline. Delirium is often caused by severe conditions like sepsis and is associated with ICU-stay and mechanical ventilation (Pandharipande et al., 2013, Saczynski et al., 2012) 3. Delirium has significant effects on cognitive decline independent of pre-existing dementia pathology (Davis et al., 2012, Davis et al., 2017).

4. Diagnosing delirium superimposed upon dementia is challenging (Morandi et al., 2017). Patients with dementia have cognitive impairment, often with disorientation, memory loss and sometimes also with behavioural and psychiatric symptoms. The cognitive symptoms or problems with behaviour often seen in delirium could thus be due to the pre-existing, chronic dementia. Further, inattention - being a core feature of delirium, is also often present in patients with dementia. The challenge of diagnosing delirium superimposed on dementia is highlighted in a survey where delirium specialist worldwide replied to how to separate delirium superimposed on dementia (DSD) from behavioural and psychological symptoms of dementia (BPSD) (Richardson et al., 2016). There was no real consensus on this topic, illustrating how difficult it is. This challenge is especially relevant in geriatric medicine and in hip-fracture patients, where the patients usually have some degree of cognitive impairment before admission. This will be further elaborated in the Discussion section.

3.2 Dementia. Definition, diagnosis and clinical features

Dementia is a chronic syndrome characterized by cognitive decline, impairment in activities of daily living and a change in social abilities and behaviour (Robinson et al., 2015).

The clinical presentation of dementia is dominated by memory impairment, decline in other cognitive abilities (e.g., language, orientation, executive functioning, judgement and thinking), behavioural changes and decline from the previous level of functioning. The most commonly used diagnostic criteria for dementia in Norway are the ICD-10 criteria (WorldHealthOrganization, 1993), see table 4. It is required that the decline in both memory and other cognitive functions is to such an extent that it significantly influences the activities of daily living.

Dementia is common in the general hospital setting and the prevalence ranges from 20 to 42% in adults over 70 years (Sampson et al., 2009, Timmons et al., 2015, Travers et al., 2013), with even higher rates in the oldest patients (Travers et al., 2013). The prevalence of dementia among hospitalized patients with delirium has been reported to be between 51 and 68% (Morandi et al., 2014). In a recent study of medical patients, 57% of patients with delirium were found to have DSM-IV dementia (Jackson et al., 2016b). None of the reported studies have been carried out in Norwegian patients, but the prevalence of dementia in hospitalised older patients is probably similar in Norway.

In this thesis, for patients classified as having dementia according to consensus diagnosis, the ICD-10 *research* criteria were used. In the methods section, there is a more detailed description of the diagnostic process used to assess whether the criteria were fulfilled in the study participants.

Table 4. ICD-10 research criteria for dementia

Evidence of each of the following:

(1) A decline in memory, which is most evident in the learning of new information, although in more severe cases, the recall of previously learned information may be also affected. The impairment applies to both verbal and non-verbal material. The decline should be objectively verified by obtaining a reliable history from an informant, supplemented, if possible, by neuropsychological tests or quantified cognitive assessments.

The severity of the decline, with mild impairment as the threshold for diagnosis, should be assessed as follows:

Mild: a degree of memory loss sufficient to interfere with everyday activities, though not so severe as to be incompatible with independent living. The main function affected is the learning of new material. For example, the individual has difficulty in registering, storing and recalling elements in daily living, such as where belongings have been put, social arrangements, or information recently imparted by family members.

Moderate: A degree of memory loss which represents a serious handicap to independent living. Only highly learned or very familiar material is retained. New information is retained only occasionally and very briefly. The individual is unable to recall basic information about where he lives, what he has recently been doing, or the names of familiar persons.

Severe: a degree of memory loss characterized by the complete inability to retain new information. Only fragments of previously learned information remain. The subject fails to recognize even close relatives.

(2) A decline in other cognitive abilities characterized by deterioration in judgement and thinking, such as planning and organizing, and in the general processing of information. Evidence for this should be obtained when possible from interviewing an informant, supplemented, if possible, by neuropsychological tests or quantified objective assessments. Deterioration from a previously higher level of performance should be established.

The severity of the decline, with mild impairment as the threshold for diagnosis, should be assessed as follows:

Mild. The decline in cognitive abilities causes impaired performance in daily living, but not to a degree making the individual dependent on others. More complicated daily tasks or recreational activities cannot be undertaken.

Moderate. The decline in cognitive abilities makes the individual unable to function without the assistance of another in daily living, including shopping and handling money. Within the home, only simple chores are preserved. Activities are increasingly restricted and poorly sustained.

Severe. The decline is characterized by an absence, or virtual absence, of intelligible ideation. The overall severity of the dementia is best expressed as the level of decline in memory or other cognitive abilities, whichever is the more severe (e.g. mild decline in memory and moderate decline in cognitive abilities indicate a dementia of moderate severity).

(3) Preserved awareness of the environment. When there are superimposed episodes of delirium the diagnosis of dementia should be deferred.

(4) A decline in emotional control or motivation, or a change in social behaviour, manifest as at least one of the following:

- (1) emotional lability
- (2) irritability
- (3) apathy
- (4) coarsening of social behaviour

(5) For a confident clinical diagnosis, (1) should have been **present for at least six months**; if the period since the manifest onset is shorter, the diagnosis can only be tentative.

3.3 The pathophysiology of delirium

3.3.1 Introduction. Direct causes and aberrant stress responses

Over the years, a number of hypotheses have been proposed as attempts to explain how a systemic disturbance (e.g. infection, surgery, trauma) can lead to the development of delirium (Maldonado, 2013). Delirium is a mental syndrome, but resulting mostly from peripheral conditions that precipitate the acute brain dysfunction (MacLullich et al., 2013). It is uncertain how this peripheral or systemic disturbance can cause a dysregulation of central neural activity, and it seems likely that numerous processes may be involved, giving the complexity of the brain and its interactions with the periphery (MacLullich et al., 2013).

Direct causes and aberrant stress responses

It has been suggested to separate the different possible pathophysiological processes into 1) the effect of direct brain insults (e.g., hypoxia) and 2) the effect of aberrant stress responses (e.g., exaggerated inflammatory responses, activation of the Hypothalamic - Pituitary - Adrenaline [HPA] axis). These direct or indirect pathways induce neurochemical abnormalities (e.g., dopamine excess or acetylcholine deficiency) contributing to the delirium symptoms.

3.3.2 Direct brain insults

Direct brain insults are acute processes that compromise the brain function directly. Some of these causes are drugs (e.g. anticholinergics, dopaminergics, opioids, benzodiazepines) directly altering the neurotransmitter levels, hypoxemia (Schoen et al., 2011, Slater et al., 2009), hypercapnia (Scala, 2011) or hypoglycaemia, or damage to the brain parenchyma (trauma, ischemia, haemorrhage, etc.) (MacLullich et al., 2008).

Common for these causes are that they cause energy deprivation and metabolic abnormalities and thus compromise brain function. These causes directly affect the brain and the oxygen delivery to the brain cells. Also the use of drugs that act directly on brain cells, like benzodiazepines and opioids, and deep sedation, are associated with an increased risk of developing delirium (van den Boogaard et al., 2012, Martinez et al., 2012, Aldecoa et al., 2017).

3.3.2.1 Hypotension - a cause of delirium?

There is some controversy about the cognitive consequences of intraoperative control of blood pressure. Intraoperative hypotension has been suggested as a predictor of postoperative delirium, (Gustafson et al., 1988, Edlund et al., 2001, Patti et al., 2011, Tognoni et al., 2011). However, the literature on this topic has shown conflicting results, as other studies did not find such an association (Williams-Russo et al., 1999, Marcantonio et al., 1998, Moller et al., 1998). Even though these studies are well-designed and some included a high number of patients (n>1000) (Marcantonio et al., 1998, Moller et al., 1998), they also have some relevant limitations. Both these studies included only patients undergoing elective surgery. Moller et al also excluded frail patients and patients with known preoperative cognitive impairment (preoperative score of 23 or less on the Mini Mental State Examination (MMSE)). Previous studies in hip fracture patients studying a possible association between intraoperative hypotension and delirium are rather small (n about 100) (Gustafson et al., 1988, Edlund et al., 2001).

3.3.3 From the periphery to the central nervous system

One of the major research questions in delirium pathophysiology is, however, how a *milder peripheral* insult can lead to delirium in predisposed individuals (MacLullich et al., 2008). When the precipitating insult leading to delirium is not very significant, as in milder peripheral infections without severe physiological disturbances, it can be assumed that the patient developed delirium in part due to *the body's response* to the insult, and not by the insult itself. This category of causes is frequently referred to as the body's "stress responses"; involving the autonomic nervous system, the HPA axis, and inflammatory pathways. These responses are hypothesised to be exaggerated in patients with delirium, thus the term "*aberrant stress responses*".

How direct brain insults and aberrant stress responses actually may lead to development of the clinical features seen in delirium is not well described.

Multiple animal studies suggest that prior neurodegenerative pathology (prion disease or cholinergic deficiency) is associated with an exacerbated response to inflammatory stimuli (both peripheral and in CNS) (Cunningham et al., 2009, Cunningham et al., 2005, Murray et al., 2012).

A leading hypothesis is that neuroinflammation is important in delirium pathophysiology (Cerejeira et al., 2014). This theory proposes that the systemic inflammation propagates into the CNS and generates neuroinflammation. The inflammatory state of a peripheral condition, eg. infection or trauma, is somehow transmitted to the CNS.

There are different theories how the peripheral state could be transduced to the CNS and trigger the development of delirium, and several mechanisms may act in parallel.

One pathway is a *neural pathway*, where peripheral molecules and inflammatory markers (cytokines) activate afferent nerves, such as the vagal nerve, that relay the afferent signals to the brain stem. (Dantzer et al., 2008).

Another hypothesis, not necessarily competing with the neural pathway, is that the peripheral inflammatory signals somehow are transferred across the *blood-brain barrier* (Zeevi et al., 2010).

A third possibility is that the peripheral signals enter via the *circumventricular region* (brain regions where the BBB is discontinuous (van Gool et al., 2010).

These communication pathways from the peripheral inflammation to the brain, might ultimately lead to the production of cytokines by microglial cells (Dantzer et al., 2008, Murray et al., 2012, Cunningham and MacLullich, 2012).

3.3.4 Neuroinflammation

Several studies have demonstrated that patients with delirium had higher *peripheral levels* of proinflammatory cytokines, such as CRP, IL-6 (de Rooij et al., 2007, van Munster et al., 2008, Plaschke et al., 2010, van den Boogaard et al., 2011, Egberts et al., 2015, Vasunilashorn et al., 2015), TNF-alpha, IL-1RA (Adamis et al., 2009), IL-10 (van den Boogaard et al., 2011) and IL-8 (de Rooij et al., 2007, MacLullich et al., 2011, van den Boogaard et al., 2011), soluble tumor necrosis factor receptor-1 (sTNFR1) (Girard et al., 2012), monocyte chemoattractant protein-1 (MCP-1) (Skrede et al., 2015) as compared with non-delirious patients. Also plasma levels of neopterin have been associated with delirium (Osse et al., 2012, Egberts et al., 2015). Lower levels of neuroprotective factors like insulin-like growth factor-1 (IGF-1) (Adamis et al., 2009, Egberts et al., 2015) have been described in patients

with delirium, as well as lower levels of plasma protein C (Girard et al., 2012). Lower levels of protein C might reflect a role of deranged coagulation, or it could result from protein C's anti-inflammatory effects (Girard et al., 2012). The results of studies of single serum inflammatory markers are inconsistent, but an imbalance between proinflammatory and anti-inflammatory factors, in favour of a proinflammatory response has been suggested (Cerejeira et al., 2012).

These findings suggest a role of inflammation in delirium, but they are only assessing the peripheral level of cytokines, not necessarily mirroring the CNS-level of inflammation.

As the CSF is closer to the brain cells, changes in CSF-levels of inflammatory mediators might reflect neuroinflammation more precisely (Blennow et al., 2010). There are only a few human studies in delirium assessing markers of inflammation in the CSF.

IL-1beta and IL-1ra (Cape et al., 2014): The pro-inflammatory cytokine CSF IL-1beta was higher in hip fracture patients (n=43) with incident delirium (n=17) compared to those without delirium, indicating a role of IL-1beta early in delirium pathogenesis. IL-1 receptor antagonist (IL-1ra) was also elevated, but only in patients who had already developed delirium. The CSF levels of IL-1beta in this study were higher than serum levels, and there was no correlation between the two, indicating a central source of IL-1beta. IGF-1 and IFN-gamma were not detected in CSF. However, as with many of the CSF studies in delirium, the sample size was small and the cross-sectional design does not allow concluding about the source or dynamics of the cytokines.

IL-6 and IL-1RA (Westhoff et al., 2013): This was an explorative study, examining 42 chemokines and cytokines by multiplex analysis. The CSF levels of IL-6 and IL-1RA were lower in patients with postoperative delirium. The IL-1RA is an inhibitor of pro-inflammatory cytokines (e.g., IL-1beta), and lower levels indicate an increased inflammatory state. No difference was found for IL-8. Moreover, a higher level of preoperative serum IL-6 was found. The discrepancy between IL-6 findings in serum and CSF is hard to interpret, and illustrates the challenge associated with a cross-sectional design: Could elevated serum IL-6 constitute an early manifestation of systemic inflammation preceding an increased neuroinflammatory response? In this study, the findings did not indicate an increased pro-inflammatory CNS activity, but rather a reduced anti-inflammatory response (lower IL-1RA).

IL-8 (MacLulich et al., 2011): Higher levels of CSF IL-8 have been demonstrated in patients with delirium after hip fracture. In this study, six cytokines were measured, but only IL-8 (33/36 samples) and IL-6 (3/36) samples were above the detection limit

Neopterin (Hall et al., 2016): Neopterin is a biomarker of cell mediated immunity. Higher CSF levels have been measured in hip-fracture patients who developed delirium compared to those who did not get delirium. The highest levels were found in patients with delirium superimposed on dementia, and the lowest levels were in patients with none of these conditions.

There has only been published one study of *repeated samples of CSF* in patients with delirium. The study included 10 patients undergoing major knee surgery (Hirsch et al., 2016). They had an indwelling spinal catheter, and samples were collected preoperatively, and 3, 6 and 18 hours postoperatively. Only one of the ten patients developed delirium, making group comparisons difficult. For all ten patients, there were elevations in several pro-inflammatory cytokines in both plasma and CSF after surgery. This study is interesting, as it shows that repeated samples of CSF is feasible, but also that it is important to control for an overall inflammatory reaction after surgery.

There are also animal studies supporting the theory that the pathophysiology of delirium involves neuroinflammation (Cunningham et al., 2005, Cunningham and MacLullich, 2012).

Microglial priming. The relationship between chronic inflammation and a cognitive response to systemic inflammation has been studied in mice (Cunningham et al., 2009). A systemic (intraperitoneal injection) challenge with lipopolysaccharide (LPS) given to mice with presymptomatic chronic neurodegenerative disease was shown to induce an exaggerated neuroinflammation (IL-1 β , TNF- α , IFN- β), as well as an acute cognitive and behavioural response, that were absent in control animals (no prion disease). Further, this study demonstrated that a single challenge with LPS was sufficient to accelerate a permanent loss of cognitive function. Thus, animal studies indicate that a transient systemic inflammation superimposed on a chronic neurodegenerative disorder will acutely exacerbate behavioural and cognitive functions, as well as accelerate disease progression.

3.3.5 Neurotransmitter hypothesis including monoaminergic activity

The neurotransmitter hypothesis describes the deficiency or abundance of certain neurotransmitters, resulting in the symptoms of delirium. Independent of other pathophysiological changes in the brain, an imbalance in neurotransmitters is most probably present, contributing to the different symptoms and clinical presentations of delirium. The most commonly described changes are excess of dopamine, noradrenaline, and glutamate, deficiency in acetylcholine and melatonin, and variable changes in serotonin, histamine and/or gamma-aminobutyric acid (GABA) (Maldonado, 2013).

It is suggested that the brain activity of other monoaminergic systems than dopamine (e.g. *serotonin*, *noradrenaline*) is increased in delirium. Support for these hypotheses comes mainly from animal studies (Qiu et al., 2016) and drug trials (Papadopoulos et al., 2014, Robinson et al., 2014).

A study of 76 elderly surgical patients (non-cardiac surgery) demonstrated higher post-operative serum levels of *noradrenaline* in patients who developed postoperative delirium (Deiner et al., 2014). This high level of noradrenaline was an independent risk factor for postoperative delirium in multivariate analyses. The levels of *cortisol* and *adrenaline* were not different between patients who developed and did not develop delirium.

Increased activity in the locus coeruleus will increase the noradrenergic activity, and might be contributing to autonomic symptoms as tachycardia, increased blood pressure, anxiety and agitation. There is evidence from drug trials (see also chapter 3.4.4) indicating that the use of α -2 adrenoceptor agonists (e.g. dexmedetomidine), inhibiting the firing of presynaptic noradrenaline neurons reduces the incidence of postoperative delirium compared to other sedatives.

3.3.6 Neuroendocrinological hypothesis and aberrant stress responses

A possible pathway from stress stimuli (psychological, pain) to the core feature of inattention in delirium, is proposed (Cunningham and MacLullich, 2012). This hypothesis suggests that stress stimuli activate the locus coeruleus, which in turn evokes higher levels of noradrenaline (NA) and dopamine (DA) in the prefrontal cortex (PFC). The concentrations of NA and DA modulate PFC functions, as working memory and attention (Arnsten, 2009). The PFC is essential in regulation of attention, inhibit inappropriate responses and regulate behaviour, thought and emotions. The PFC has connections to the monoaminergic cell bodies in the brain stem (such as locus coeruleus and the substantia nigra). In response to stress stimuli, the regulation of attention might switch from a thoughtful “top-down”

control to a more instinctive “bottom-up control” (Arnsten, 2009). The organism will respond to challenges that threaten the body's homeostasis, like injury or infection. This stress response includes (but is not limited to) the HPA-axis (including cortisol) and the sympathetic adrenal medullar (SAM) system.

3.3.7 The autonomic nervous system and hemodynamic regulation

The autonomic nervous system (ANS) regulates the unconscious and involuntary functions of internal organs to maintain homeostasis (Brodal, 2013, Goldstein, 2001). The afferent, sensory part of the ANS is transmitting information from receptors in the internal organs to the central nervous system (CNS). The efferent actions of ANS constantly adjust smooth muscles, heart muscles and glands. The most important areas in the CNS involved in autonomic control are located in the medulla oblongata and hypothalamus. These areas also communicate with other brain centres involved in cognitive processes and endocrine control. An area of particular interest is the rostral ventrolateral medulla (RVLM) in medulla oblongata. The RVLM receives inputs from baroreceptors and directly controls preganglionic sympathetic neurons, and is a vital part of the baroreceptor reflex. In addition, RVLM connects with other central areas as locus coeruleus (LC) in pons, amygdala in the limbic system and with the paraventricular nucleus in hypothalamus. The neurons in LC project extensively to all brain areas. LC probably participates in the regulation of consciousness and sleep, and seems to be important for attention (Brodal, 2013, Goldstein, 2001).

There are two different branches of the efferent part of the ANS: the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). The PNS controls mainly the conservative, vegetative processes, whereas the SNS controls the “emergency” reactions when internal homeostasis is threatened. The two systems often have the opposite effects on target organs, but the interactions between them are complex and dynamic.

Parasympathetic preganglionic neurons emanate in nuclei in the brain stem and in the sacral spinal cord. The main neurotransmitter for the postganglionic neuron at the target cell is acetylcholine. The sympathetic preganglionic neurons emanate from the intermediolateral column of the thoracolumbar spinal cord. The main neurotransmitter for the postganglionic sympathetic neuron is noradrenaline. However, in the adrenal medulla, which is controlled by preganglionic sympathetic neurons, the hormone producing cells secrete epinephrine (adrenaline), a chemical compound that functions as a hormone and not as a neurotransmitter. Thus, the physiological effects of the adrenal medulla are not identical to the rest of the sympathetic nervous system. Noradrenaline binds to receptor proteins (adrenoceptors), labelled alpha and beta. Subtypes are described, having different functional properties. Alpha-2 adrenoceptors are mostly found presynaptically at sympathetic neurons and also in the CNS, and are important for negative feedback-regulation. The binding of noradrenaline to these receptors attenuates sympathetic nervous activity (Brodal, 2013, Goldstein, 2001).

There are three different ways of assessing autonomic nervous activity: to measure the nerve activity (neurography), to measure plasma levels of neurotransmitters, or to measure end organ activity such as cardiovascular responses (Goldstein et al., 2002, Goldstein, 2001, Freeman, 2006). In this thesis (paper III) the last method was used in a study of cardiovascular responses during a head-up tilt-test, including analyses of heart rate variability, as presented in chapter 7.6.2 and discussed in chapter 9.3.3.

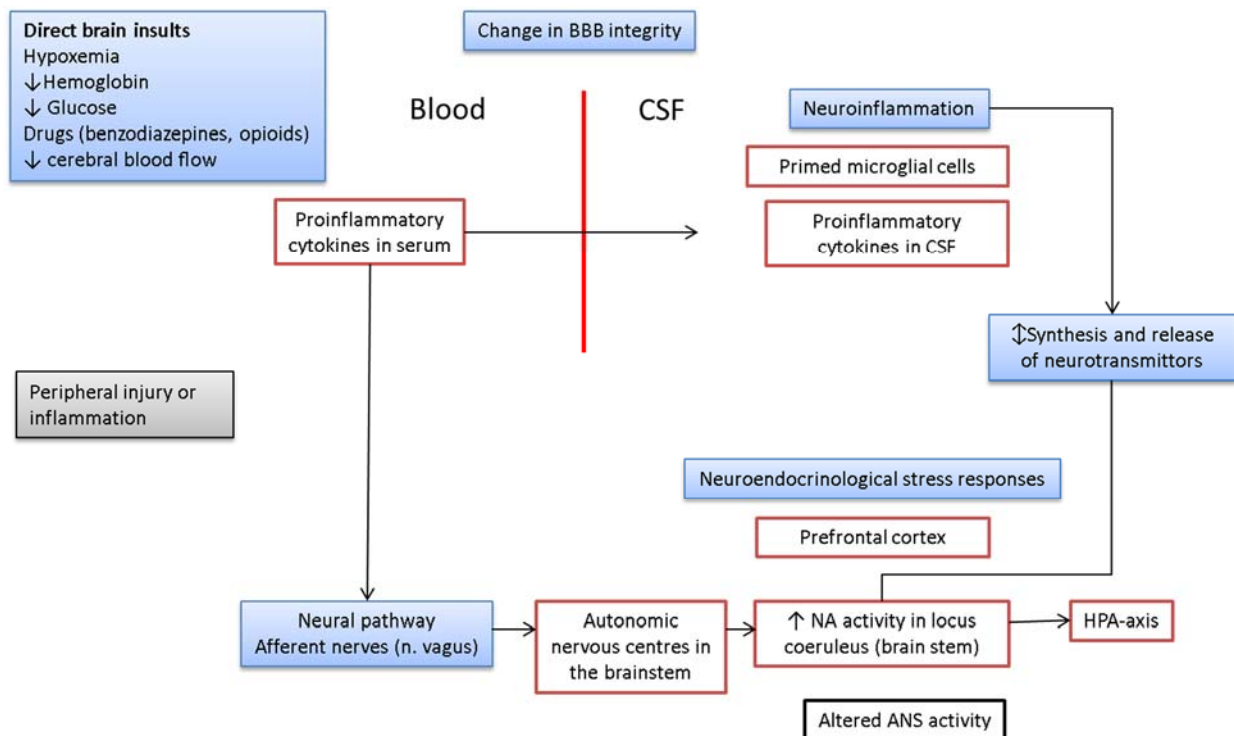
3.3.7.1 Previous studies of autonomic cardiovascular control in delirium

Few studies have assessed the role of the autonomic nervous system in patients with delirium. There is one published study by Zaal and co-workers (Zaal et al., 2014). They investigated the heart rate variability (HRV) in 25 patients treated in an intensive care unit (ICU), and did not find any significant differences in HRV parameters between ICU patients with (n=12) and without (n=13) delirium.

There are other relevant studies of HRV in elderly patients. The overall HRV decreases with age (Almeida-Santos et al., 2016), and is negatively associated with frailty status (Parvaneh et al., 2015). Further, there is evidence that reduced HRV is associated with cognitive impairment (Zeki Al Hazzouri et al., 2014, Kim et al., 2006, Femminella et al., 2014, Mahinrad et al., 2016). The study presented in paper III included geriatric patients with an acute infection. It is therefore relevant that HRV is also found to be inverse related to biomarkers of inflammation, such as C-reactive protein (CRP) (Huang et al., 2016, Papaioannou et al., 2009).

Figure 2. Some proposed pathways linking peripheral insults to CNS changes hypothesized to lead to delirium.

Elements in blue represent suggested pathophysiological pathways; elements in red represent some possible CNS structures and mediators involved in delirium.



3.4 Pharmacological prevention and treatment of delirium

Prevention and treatment of delirium is resource demanding, and should integrate medical care, multidiscipline patient care and also involve health care management and organization of health care services. It could be argued that many of the interventions are simply operationalized versions of good basic medical and nursing care.

Non-pharmacological multicomponent interventions are widely accepted as the best and most effective strategy to prevent delirium (Young et al., 2010, Hshieh et al., 2015, Inouye et al., 2014, Siddiqi et al., 2016).

Selected drug trials for prevention (table 20) and treatment (table 21) of delirium are presented in the Appendix.

There are no approved drugs for the treatment of delirium, but clinical guidelines recommend the use of low-dosage antipsychotics to treat severe behavioural symptoms and distress, if non-pharmacologic approaches are insufficient (Young et al., 2010). Antipsychotics are the most frequently used drugs to treat distressing symptoms (e.g., delusions and hallucinations) and behavioural problems (e.g., agitation) in delirious patients (Morandi et al., 2013). However, the evidence supporting this use is weak (Schrijver et al., 2016, Neufeld et al., 2016, Siddiqi et al., 2016).

Different pharmacological strategies have been tried in studies of prevention and treatment of delirium. Most of them are based on hypotheses that the balance between the levels of different neurotransmitters is disturbed in patients with delirium (Steiner, 2011). The drugs most often considered are antipsychotics, acetylcholine esterase inhibitors, and benzodiazepines, but the latest years also the alpha-2-adrenoceptor agonist dexmedetomidine and the hormone melatonin have been studied. Benzodiazepines are frequently used as a sedative strategy, but there is currently no evidence that can support their use in delirium care (Lonergan et al., 2009).

There have been some drug trials with agents not affecting the neurotransmitters directly. Some of these drugs carry anti-inflammatory properties, based on the theory that neuroinflammation is central in the delirium pathology.

Delirium pathophysiology is complex, and single pharmacological interventions might always struggle to have a meaningful impact. Even if pharmacological agents have compelling basic research and preclinical data, they might fail to demonstrate any convincing effect in the messy reality of delirium (Quinn, 2016).

In general, the drug trials in delirium are heterogeneous, studying different populations. Most trials are carried out in surgical patients or in intensive care units, and there are only a few trials studying older medical patients. *Treatment* trials usually included a low number of participants, and very few trials were randomised and placebo controlled (RCTs). Studies often have compared different drugs (e.g., first generation vs newer antipsychotics), but rarely with placebo. The methods used for delirium assessment vary across the studies, making direct comparisons difficult. The trials are also assessing different aspects of delirium (e.g., severity or duration), and at different time points throughout the course.

Drug trials for *preventing* delirium are more often placebo controlled, some also with a larger number of included patients. Antipsychotics are most often studied, but also cholinesterase inhibitors, melatonin and modification of sedation strategies are evaluated.

3.4.1 Antipsychotics

Haloperidol (Kalisvaart et al., 2005, Wang et al., 2012, Page et al., 2013) and other antipsychotics (olanzapine (Larsen et al., 2010), risperidone (Prakanrattana and Prapaitrakool, 2007) and quetiapine (Tahir et al., 2010) are commonly used in delirium management, although the evidence of their efficacy is weak (Neufeld et al., 2016).

Recently published reviews (ref Schrijver 2015 and Neufeld 2016) state that the current evidence does not support the routine use of antipsychotic drugs for prevention or treatment of delirium. For patients with parkinsonism or dementia with Lewy Bodies, antipsychotics should be avoided, leaving few treatment options for these patients.

Antipsychotics have several drawbacks; including an increased risk of death and cardiovascular events, sedation, falls risk, and cognitive impairment (Murray-Thomas et al., 2013). These risks increase with age, dementia and disability. This calls for special caution for patients with delirium superimposed on dementia (Lonergan et al., 2007, Maust et al., 2015, Maust and Kales, 2016).

3.4.2 Acetylcholinesterase inhibitors

There is no clear evidence of the efficacy of acetylcholinesterase inhibitors (AChE) in the treatment of delirium (van Eijk et al., 2010, Overshott et al., 2008, Overshott et al., 2010, Tampi et al., 2015). AChEs have hardly been studied in medical or geriatric patients. A very small study (n=15) showed no effect of rivastigmine over placebo on the duration of delirium (Overshott et al., 2010).

There are a few studies of AChEs as prevention of delirium. One study of rivastigmine taken orally (Gamberini et al., 2009) and two studies of donepezil (Liptzin et al., 2005, Sampson et al., 2007) showed no significant difference in delirium incidence between active drug and placebo. However, in a recent trial in hip-fracture patients with pre-fracture cognitive impairment, treatment with a rivastigmine 4.6 mg patch from admission to day 7 postoperatively resulted in a lower incidence of delirium compared to placebo (Youn et al., 2016). This might indicate that in the subgroup of patients with chronic cognitive impairment, there could be a preventive effect of these drugs on delirium occurrence.

3.4.3 Other drugs

Also some other drugs for the prevention or treatment of delirium have been studied. Six studies have evaluated the effect of melatonin, ramelteon or L-tryptophan on delirium incidence, with conflicting results (Walker and Gales, 2016). Postoperative administration of ondansetron (a 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist) or placebo in 106 hip-fracture patients resulted in lower incidence and shorter duration of delirium in the ondansetron group (Papadopoulos et al., 2014). A study of rosuvastatin (a statin) showed no benefit in reducing delirium in ICU-patients (Needham et al., 2016). Anti-inflammatory drugs as dexamethasone (Sauer et al., 2014) and methylprednisolon (Whitlock et al., 2015) have been investigated, but no beneficial effect on delirium was found. A small study (n=21) indicated a promising effect of gabapentin on delirium incidence

(Leung et al., 2006). Pregabalin given before cardiac surgery (n=70) reduced the CAM-ICU scores on postoperative day 1, but not the following days, compared to placebo (Pesonen et al., 2011).

Benzodiazepines and other sedatives (as chlomethiazole) are also frequently used in delirious patients, but the evidence supporting these agents is even weaker than for the drugs already presented (Clegg and Young, 2011, Lonergan et al., 2009). Several psychotropic drugs have side effects that may be serious in frail, elderly patients, eventually precipitating, worsening or prolonging delirium (Clegg and Young, 2011).

3.4.4 Alpha-2 adrenoceptor agonists

Dexmedetomidine, an alpha-2 adrenoceptor agonist, decreases sympathetic activity and attenuate the hemodynamic and neuroendocrine stress responses (including of cortisol), resulting in decreased heart rate (HR) and blood pressure (BP) as well as sedative and analgesic effects (Uyar et al., 2008).

In the intensive care setting, both dexmedetomidine and clonidine reduce the need for opioids and sedatives (Pichot et al., 2012). Dexmedetomidine is increasingly used in intensive care patients, and also as an adjuvant drug during regional anaesthesia (Keating, 2015). Several studies indicate that the incidence of delirium is lower in intensive care patients receiving dexmedetomidine than in those receiving benzodiazepines (Pandharipande et al., 2007, Riker et al., 2009), propofol (Maldonado et al., 2009) or morphine (Shehabi et al., 2009). Currently available evidence thus suggests that dexmedetomidine may have value in the prevention and treatment of delirium in the intensive care unit (Mo and Zimmermann, 2013, Zhang et al., 2013). Indeed, it is now in clinical use in the USA and Europe (Bajwa and Kulshrestha, 2013).

There is, however, uncertainty whether the possible effect of dexmedetomidine on delirium is due to less use of deliriogenic sedatives or a possible direct anti-delirium effect of dexmedetomidine (Chen et al., 2015).

3.5 Clonidine

Dexmedetomidine and clonidine are both alpha-2 adrenoceptor agonists activating presynaptic inhibitory alpha-2 adrenoceptors. They exert a general inhibitory influence on the sympathetic nervous system, in particular due to CNS effects (Smith and Elliott, 2001). Most patients with delirium are treated outside intensive care units, where intravenous use of dexmedetomidine is not feasible. An alternative agent to dexmedetomidine might be orally administered clonidine, which has very similar pharmacodynamics properties to that of dexmedetomidine (Pichot et al., 2012), even though its alpha-2 selectivity is somewhat lower (Khan et al., 1999). In addition, clonidine has an independent stimulatory effect on the parasympathetic activity and a slight anti-inflammatory effect (Cividjian et al., 2011, Kim and Hahn, 2000), further making it an interesting candidate for delirium treatment, cf. the hypothesis of delirium as a consequence of aberrant stress responses (MacLulich et al., 2008).

3.5.1 Previous clinical experience

Clonidine has been used as an anti-hypertensive drug for decades, as well as for anaesthesia-related applications, such as perioperative analgesia (Smith and Elliott, 2001, Blaudszun et al., 2012), sedation and anxiolysis, and for management of both acute postoperative, chronic and neuropathic pain (Blaudszun et al., 2012, Wright et al., 1990, Laurito et al., 1991). Clonidine is sedative in small doses. Clonidine 0.3 mg orally has shown a sedative and anxiolytic effect in young women (Wright et al., 1990), and even as low dose as 0.1 mg had a small sedative and anxiety reducing effect, given as premedication before anaesthesia (Laurito et al., 1991).

Clonidine in delirium is poorly studied, but a pilot study (N=30) showed that the use of clonidine infusion (0.5 µg/kg bolus, then 1-2 µg/kg/t) during the weaning period after surgery for type-A aortic dissection might reduce the severity of delirium, improve respiratory function and shorten length of ICU stay (Rubino et al., 2010). We designed LUCID (The Oslo Study of Clonidine in Elderly Patients with Delirium) to investigate potentially positive effects of clonidine upon delirium in a more unselected population of geriatric inpatients.

Safety issues and adverse effects of clonidine

The adverse effects of clonidine include orthostatic hypotension, bradycardia and AV-block. Such effects are, however, dependent on dosage. In a previous report, low-dose treatment (75 µg) in healthy adults was associated with a reduction in mean heart rate from 72 to 63 bpm, and a reduction in MAP from 88 to 75 mmHg. Less than 50% experienced sedation, dry mouth or dizziness, and for those who reported any of these side-effects, the severity was mild (Anavekar et al., 1982). Clonidine has been studied in outpatients with Alzheimer's dementia (Mohr et al., 1989, Davidson et al., 1989) and in patients with Parkinson's disease (Riekkinen et al., 1999, Serrano-Duenas, 2003). Treatment with daily doses of clonidine less than 200 µg was well tolerated in these patients.

Relative contraindications to clonidine for its licensed indications include bradyarrhythmias, polyneuropathy, renal insufficiency and evidence of reduced cerebral and/or peripheral circulation due to vessel disease.

Some studies have addressed myocardial ischemia and safety of clonidine administration: A single oral dose of clonidine, 2 µg/kg can reduce perioperative myocardial ischemic episodes (vascular surgery and non-cardiac surgery). These low dosages (0.2 mg orally in non-cardiac surgery) did not affect the hemodynamic stability (Stuhmeier et al., 1996, Wallace et al., 2004). A meta-analysis has suggested that clonidine given pre- or intra-operatively reduces myocardial ischemic episodes without increasing the incidence of bradycardia. Clonidine seems to improve the myocardial oxygen balance (Nishina et al., 2002).

Clonidine has the following known drug interactions:

- Monoamine reuptake inhibitors in combination with clonidine may cause risk of severe hypertension
- Clonidine can cause increased effect of ciclosporin
- Tricyclic antidepressants cause decreased antihypertensive effect of clonidine
- The effect of other antihypertensive drugs (diuretics, vasodilators, calcium-antagonists, ACE-inhibitors) can be enhanced by clonidine
- The effect of drugs with negative chronotropic effect (beta-blockers, calcium-antagonists or digitalis) can be enhanced by clonidine
- The hypertensive reaction to withdrawal of clonidine can be enhanced by beta-blockers.
- Clonidine has an additive effect when combined with other drugs causing depression or tranquilization of the central nervous system
- Alpha-2-receptor blockers (phentolamine, tolazoline) can reverse the effect of clonidine

3.5.2 Pharmacokinetics and rationale for dosage plan of clonidine in LUCID

Maximum plasma concentration (C_{max}) of clonidine following oral administration occurs after 1-3 h (Anavekar et al., 1982). Anavekar found that peak levels of clonidine after one single dose were reached between 2.4 and 2.9 hours. Reduction in mean arterial pressure as well as the risk of side effects is highest at this peak. C_{max} and area under the concentration-time-curve (AUC) increase proportionally with increasing doses. Clonidine traverses the blood–brain-barrier. The half-life during the elimination phase shows great inter-individual variation and is found to be between 5 and 25.5 hours. The metabolism is hepatic and the metabolites are inactive. Clonidine is mainly excreted renally (70%).

Concentration levels of clonidine known to have clinical effects range from 0.2 to 2.0 ng/ml (Almenrader et al., 2009, Hogan et al., 1981, Keranen et al., 1978). In planning of the LUCID study we were aiming for the lower levels, that is, between 0.3 ng/ml (median trough concentration) and 0.7 ng/ml (maximal concentration), because higher plasma concentration levels increases the risk of adverse events, including hypotension. On the other side, lower plasma concentration levels may be insufficient to give a significant effect on our primary endpoint.

To our knowledge, there are no studies of the relationship between plasma concentration of clonidine and delirium. In publications on the effect on delirium of dexmedetomidine, the plasma concentration levels are not reported. Additionally, dexmedetomidine is approximately 8 times more

selective (alpha 2 versus alpha 1) than clonidine (Khan et al., 1999, Pichot et al., 2012), so pharmacokinetic data on dexmedetomidine cannot be used to estimate effective doses of clonidine. We thus had to extrapolate from pharmacokinetic data on clonidine used for other purposes (See table 5). We know that clonidine has both sedative and anxiolytic effects, and that these centrally mediated effects are closely related to plasma concentration levels (Davies et al., 1977, Frisk-Holmberg et al., 1978).

In a study of adolescents with chronic fatigue syndrome, a dosage of 50 µg twice per day resulted in a median trough concentration (C_0) at 0.21 µg/L after 14 days of treatment, rising to a median level of 0.41 µg/L (C_{max}) two hours after administration of one regular dose of 50 µg (Sulheim et al., 2014, Fagermoen et al., 2012).

In a study of healthy normotensive subjects, treatment with oral clonidine 225 µg daily (75 mcg x 3) for one week resulted in a steady state of 0.3-0.35 ng/ml (Keranen et al., 1978). After intake of one 75 µg tablet, the serum level increased to 0.7 ng/ml at 2 h. A significant relationship between the plasma level of clonidine and sedation was reported.

In persons receiving oral clonidine 100 µg twice per day for 6 weeks, plasma concentration ranged between 0.4 and 0.7 ng/ml (levels 2 hours after intake of 100 µg) (Hogan et al., 1981). There were almost no changes in sBP sitting, but a fall of sBP up to 10mmHg standing.

Another study found that a single dose of 75 µg gave a C_{max} of 0.66 ng/ml after achieving steady-state with two 75 µg doses (Anavekar et al., 1989).

Table 5. Studies of plasma concentration levels of clonidine

Author, year	Dose	C null (steady state), µg/L	Duration of treatment before measurement C null	C max, µg/L, measured 2-3 hours after intake
Fagermoen 2012	50 µg x 2	0.2	14 days	0.4
Keranen	225 µg x 1	0.3	7 days	0.7
Hogan 1981	100 µg x 2	0.4	6 weeks	0.7
Anavekar 1989	75 µg x 2		5 days	0.66
Anavekar 1989	75 µg one dose		3.6 hours	0.34

C null = median trough concentration; C max = maximum plasma concentration

We expected our patient population to have a longer half life of clonidine due to a diminished renal capacity as compared to younger. Although the metabolism of clonidine is hepatic, varying amounts of unmetabolised clonidine is secreted renally. Consequently, our patients might have a higher risk of adverse events related to the study drug. For safety reasons, we therefore chose a lower dosage of 75 µg twice per day.

Loading doses

Since we studied short-term use in an acute setting, we wanted to achieve steady-state quicker by using loading doses under close monitoring of blood pressure. The loading dose is based on half-life. Clonidine follows first order kinetics for elimination, and thus the mean steady state is proportional

to the daily dose. Doubling the total daily dose should double the mean plasma concentration level. A previous study had showed that a single oral dose of 75ug clonidine gave C_{max} 0.29 ng/ml, 150ug gave C_{max} 0.61 ng/ml and 250ug gave 1.2 ng/ml (Anavekar et al., 1982). We decided to administer up to 300 µg the first day, but as 75 µg every three hours. Thus, the theoretical C_{max} at day one was expected to be significantly lower than 1.2 ng/ml, due to elimination of the drug. How much lower was difficult to estimate, given the large variability in half-life (5 to 25 hours).

The expected maximum hypotensive effect correlates well with the C_{max} time-point occurring after 2-3 hours. There is an inter-individual difference in the pharmacodynamic response to clonidine. Thus, we decided to make our loading dose dependent on and monitored by the individual patients' haemodynamic response (blood pressure and heart rate).

4 Knowledge gaps

As described more detailed in the previous sections, numerous knowledge gaps exist regarding the pathogenesis of delirium and pharmacological treatment options. Some specific of these knowledge gaps are particularly outlined here, as they constituted the background for important strategical choices when the present research project was planned.

Two of the leading hypotheses regarding pathophysiology focus on neuroinflammation and acute stress (see also chapter 3.3).

Most previous studies of inflammatory markers and their possible associations with delirium, have measured these markers in peripheral blood, and not in CSF. A possible association between delirium and inflammatory markers (like CRP and IL-6) in CSF remained to be established (see also chapter 3.3.4).

It has been suggested that in delirium, there are aberrations in acute stress responses, involving alterations in the autonomic nervous system (ANS) activity (see also chapter 3.3.6 and 3.3.7). However, alterations in ANS activity, including autonomic cardiovascular control, are not previously well studied in delirious patients. There has also been some controversy regarding the possible impact of intraoperative control of blood pressure upon acute (delirium) and long term (dementia) cognitive decline (see also chapter 3.3.2.1).

Few documented pharmacological treatment options of delirium exist (see also chapter 3.4).

Dexmedetomidine, a parenterally administered alpha2-adrenergic receptor agonist which attenuates sympathetic nervous system activity, has shown promise as treatment of delirium in the intensive care unit (ICU) (see also chapter 3.4.4). Another alpha2-adrenergic receptor agonist, clonidine, can be administered orally, and investigating clonidine as a potential treatment of delirium seemed prudent. Such a trial would increase the knowledge of pharmaceutical treatment options in delirium, as well as give insight into possible underlying disease mechanisms. However, there have been no studies on safety of clonidine and its hemodynamic effects in geriatric hospitalized patients with delirium (see also chapter 3.5).

5 Aims

Based on these knowledge gaps, the overall aim for this thesis was:

To study disease mechanisms and treatment options in delirium, with emphasis on neuroinflammation and autonomic nervous activity.

The specific aims for each paper were:

- I. To investigate whether delirium in patients with hip fracture is associated with high CRP, IL-6, and sIL-6-R levels in CSF. (Paper I)
- II. To investigate possible associations between perioperative hemodynamic changes, use of vasopressor drugs, risk of delirium and risk of new-onset dementia. (Paper II)
- III. To explore autonomic cardiovascular control in elderly patients with and without delirium, and particularly to assess possible differences in heart rate variability according to delirium status. (Paper III)
- IV. To design and initiate a randomised placebo controlled trial investigating treatment of delirium with the alpha-2 adrenoceptor agonist clonidine. (Paper IV)
- V. To investigate the plasma concentrations and hemodynamic effects of clonidine in elderly patients with delirium, and to evaluate the dosage regime in the LUCID study. (Paper V)

6 Material/participants

The participants included in this thesis are from five different patient samples (numbered 1 to 5, see figure 3). I was responsible for recruiting the participants and collecting the data in sample 4 and (together with PhD student Karen Roksund Hov) in sample 5. I was not involved in the planning or recruitment of patients in sample 1 to 3. Sample 4 and 5 will therefore be described more detailed than sample 1 to 3. Most of the patients in sample 4 and 5 were included at the acute geriatric ward at Oslo University Hospital, Ullevål. These patients are acutely admitted, arriving directly from the emergency room. They are usually frail, the average age is above 80 years, and they have considerable multimorbidity and polypharmacy. There is a high prevalence of infections, dehydration, acute cardiac problems, general medical problems, functional decline and delirium among these patients. They are treated and taken care of by a multidisciplinary team, including nurses, physiotherapists, occupational therapists, and doctors specialised in geriatric medicine.

6.1 Participants in sample 1 (Juliebo/Krogseth)

364 participants were recruited among hip fracture patients admitted to Ullevål and Diakonhjemmet hospitals in Oslo from September 2005 through December 2006. Two researchers and three study nurses were responsible for identifying patients with hip fracture on a daily basis. All patients acutely admitted with a hip fracture (femoral neck, trochanteric or sub-trochanteric) were eligible for inclusion. Patients were excluded if the hip fracture resulted from high-energy trauma or if they were considered as moribund by the orthopaedic surgeon at admission. Patients from nursing homes and patients with dementia were *not* excluded. Patients < 65 years and patients with a length of hospital stay of < 48 hours were excluded (Juliebo et al., 2009). 174 patients of the patients included in sample 1 were assessed 6 months after surgery by one single physician (Krogseth et al., 2011).

6.2 Participants in sample 2 (Watne)

332 hip fracture patients were recruited from September 2009 through January 2012 at Oslo University Hospital, Ullevål. These patients were included in a RCT; Oslo Orthogeriatric Trial (OOT) (Watne et al., 2014). The primary aim in this RCT was to compare orthogeriatric care with usual orthopaedic care. Delirium incidence was a secondary outcome and was equal between the groups. The patients were assessed 4 and 12 months after the fracture by research nurses. 3 patients were erroneously recruited and were excluded from the RCT, because they were moribund at admission and thus did not fulfil the selection criteria. CSF from 99 patients in sample 2, collected at the onset of anaesthesia, was used for analyses in paper 1.

6.3 Participants in sample 3 (Hall)

108 hip fracture patients were included from September 2009 through April 2011 at the Royal Infirmary, Edinburgh, Scotland. The participants were recruited by a geriatrician (Roanna Hall) in the Orthopaedic Unit, and closely monitored for delirium during the perioperative period. CSF from 52 patients in sample 3, collected at the onset of anaesthesia, was used for analyses in paper 1. The study design was similar to sample 1 and 2, with the same methods used for assessment of delirium (CAM) and pre-fracture cognitive decline (IQCODE).

6.4 Participants in sample 4 (Neerland)

14 participants were recruited between March 2012 and January 2015 among patients acutely admitted to the acute geriatric ward at Oslo University Hospital, Ullevål. Patients were eligible if they had an acute, ongoing infection. Both patients with and without delirium were included. Patients who were taking adrenergic antagonists, antiarrhythmics or acetylcholine esterase inhibitors, or who had atrial fibrillation or used a cardiac pacemaker, were excluded. If they did not have any exclusion criteria, they were asked by the investigator (BEN) to participate in a head-up tilt-test (HUT) the next morning, between 9 and 10 a.m., performed by the same investigator. The HUT took place some days after admission, to ensure that the patients were rehydrated and that initial medical treatment was started.

6.5 Participants in sample 5 (Neerland/Hov)

20 study participants were recruited from patients above 65 years acutely admitted to the medical department at Oslo University Hospital, Ullevål, between 10 April 2014 and 1 February 2017. We routinely screened all patients admitted to the geriatric ward, and from January 2015 we also screened patients admitted to the acute medical observation unit and to the general internal medical ward. The stroke unit is also a part of Department of Geriatric Medicine at Ullevål hospital, and some of the patients admitted there do not have stroke, but other acute medical conditions. Because the inclusion in LUCID went very slowly, we looked for eligible study participants also in the stroke unit. 17 of the included patients were recruited from the acute geriatric ward, and 3 patients were recruited from the acute medical observation unit. We did no screening during the weekends and during some summer holiday weeks. The patients were assessed 4 months after hospital discharge by one of the study physicians (KRH, BEN), but these data are not yet analysed and will not be presented in this thesis. The screening process, selection criteria and randomisation of patients are described more detailed in chapter 7.1.

6.6 The selection of patients in the different studies

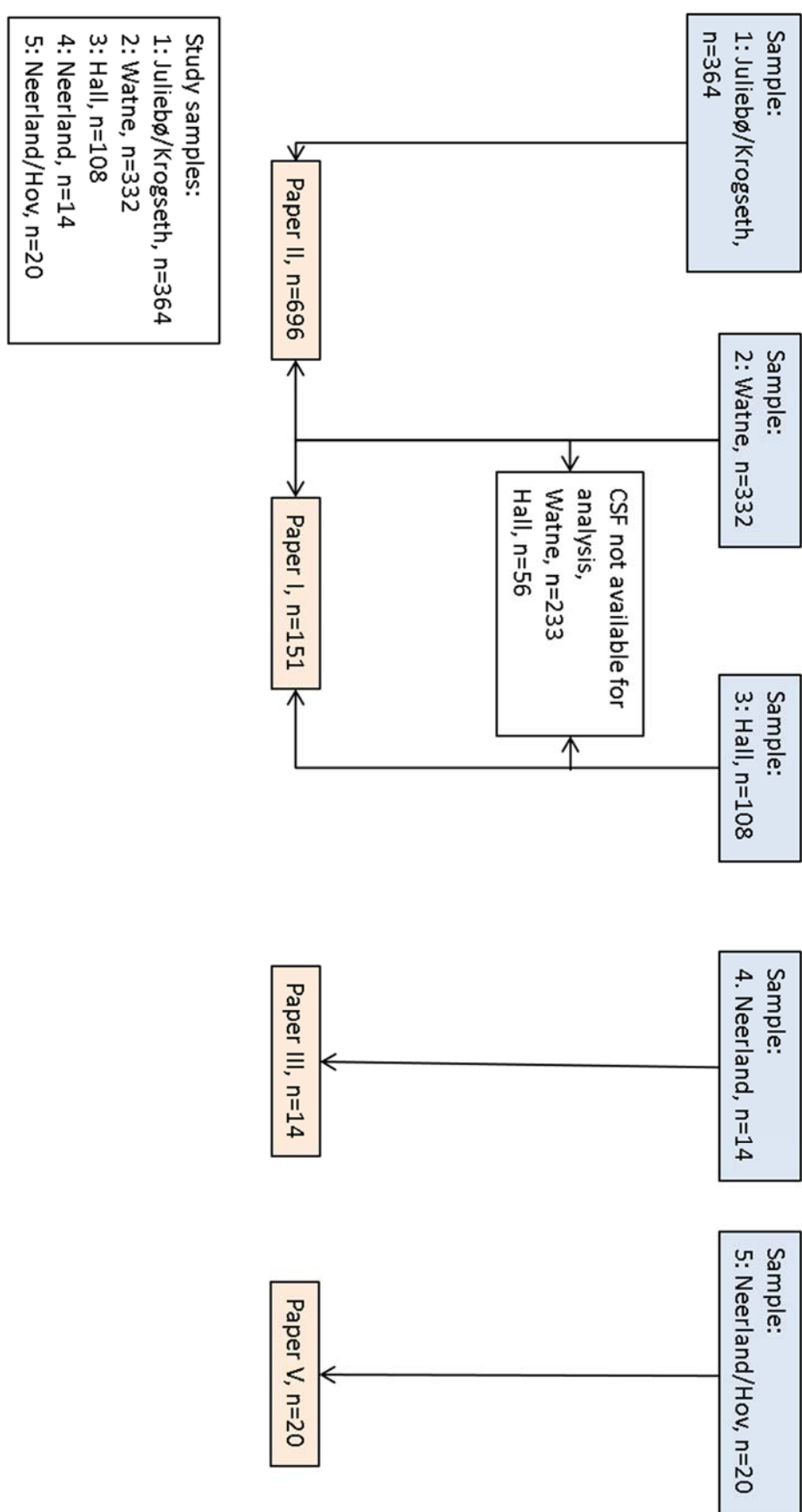
Paper I: The study included hip-fracture patients from sample 2 (Watne, n=99), and sample 3 (Hall, n=52) with CSF available.

Paper II: The study included hip-fracture patients from sample 1 (Juliebø/Krogseth, n=364) and sample 2 (Watne, n=332)

Paper III: The study included geriatric patients with an acute infection from sample 4 (Neerland, n=14)

Paper V: The study included geriatric patients with delirium from sample 5 (Neerland/Hov, n=20)

Figure 3. Selection of patients in the different papers



7 Methods

7.1 Study design of The Oslo Study of Clonidine in Elderly Patients with Delirium (LUCID)

The Oslo Study of Clonidine in Elderly Patients with Delirium (LUCID) was designed as a randomised, placebo-controlled, double-blinded, parallel group study with 4-month prospective follow-up [Paper IV]. Patients were randomised to orally administered clonidine or placebo until delirium free (by DSM-5 criteria) or no subsyndromal delirium for 2 days, or after a maximum of 7 days treatment.

7.1.1 Selection of patients in LUCID

Acutely admitted medical patients > 65 years with delirium or subsyndromal delirium were eligible for inclusion. The selection criteria are presented in table 6.

Patients with chronic cognitive impairment or dementia were not excluded, and nursing home patients were also eligible. Patients > 65 years were screened, though we expected the average age to be more than 80 years. The patient had to be willing and able to receive the study medication and to cooperate voluntarily.

Table 6. Criteria for inclusion and exclusion in the LUCID study

Inclusion criteria

All of the following conditions had to apply to the prospective patient at screening prior to receiving study agent:

- Patient > 65 years old admitted to the acute, medical, geriatric ward *
- Delirium or subsyndromal delirium within the last 48 hours
- Signed informed consent from patient or relatives and expected cooperation of the patients for the treatment and follow up must be obtained and documented

Exclusion criteria

Patients were excluded from the study if they met any of the following criteria:

- Symptomatic bradycardia, bradycardia due to sick-sinus-syndrome, second- or third- degree AV-block (if not treated with pacemaker) or any other reason causing HR <50 bpm at time of inclusion.
- Symptomatic hypotension or orthostatic hypotension, or a systolic BP <120 at the time of inclusion
- Ischemic stroke within the last 3 months or critical peripheral ischemia
- Acute coronary syndrome, unstable or severe coronary heart disease (symptoms at minimal physical activity; NYHA 3 and 4) and moderate to severe heart failure (NYHA 3 and 4). (Acute coronary syndrome is defined according to international guidelines)
- A diagnosis of polyneuropathy, pheochromocytoma or renal insufficiency (estimated GFR < 30 ml/min according to the MDRD formula)
- Body weight <45 kg

- Considered as moribund on admission
- Unable to take oral medications
- Current use of tricyclic antidepressants, monoamine reuptake inhibitors or ciclosporin
- Previously included in this study
- Adverse reactions to clonidine or excipients (lactose, saccharose)
- Not speaking or reading Norwegian
- Any other condition as evaluated by the treating physician
- Admitted to the ICU **

In December 2014 the selection criteria were slightly amended, to :

* Patient > 65 years old acutely admitted to *the medical department*

** Patients admitted to the ICU could not be included.

7.1.2 Randomization and blinding

The randomization was based on computer-generated random numbers (in a 1:1 ratio for active: placebo). The randomization scheme was distributed to the producer of the study drug in Kragerø, and they made capsules according to this scheme. BEN and KRH (the investigators) were blinded to the randomization scheme. The placebo capsule and the capsule with clonidine looked identical.

Figure 4. Study drug (IMP) - either clonidine or placebo



The participants were randomized in two separate strata; those who were referred from nursing homes and those who were not. There was a 1:1 randomization to placebo and active medication in each group. The patients were also randomized in blocks of 10 patients in each stratum separately.

It is not feasible to make strata for all risk factors for delirium. We chose admittance from nursing home as our stratification variable, as a practical substitute for cognitive decline and level of functioning.

For each study participant there was a sealed envelope with the randomization code. The code for a particular subject could be broken in a medical emergency, if knowing the identity of the treatment allocation would influence the treatment of the subject.

7.1.3 Screening of patients for inclusion in LUCID

The following is a description of the procedures used for assessment of patients for inclusion in LUCID (paper IV-V):

Originally, only patients >65 years of age admitted to the acute geriatric ward could be recruited in LUCID. However, we changed the selection criteria in December 2014, and started recruitment of patients also from other medical wards. This was because of a very low inclusion rate. The main reason for the low inclusion rate was that very many eligible patients fulfilled one or several exclusion criteria (e.g., admitted to hospital because of worsening of heart failure, hypotension, etc.). The problems regarding inclusion are discussed more detailed in chapter 9.3.5.

Table 7. Screening for delirium in LUCID

		Yes	No
Screening	SQID *	<input type="checkbox"/>	<input type="checkbox"/>
	Drowsiness	<input type="checkbox"/>	<input type="checkbox"/>
	Cannot recite months backwards (unable to reach July)	<input type="checkbox"/>	<input type="checkbox"/>
	Cannot recite all the weekdays backwards	<input type="checkbox"/>	<input type="checkbox"/>
	Staff suspect delirium	<input type="checkbox"/>	<input type="checkbox"/>
Ascertainment of delirium or subsyndromal delirium	If Yes in any box, do diagnostic procedure (DSM-5)		
Inclusion	All DSM-5 criteria (delirium) or subsyndromal delirium → can be included		
	If the patient meets all the inclusion criteria, the patient will be included		

* SQID = Single Question in Delirium

The screening procedure was a combination of the Single Question in Delirium (SQID) (asking one question to the patient's friend or relative: "Do you think (name) has been more confused in the last two weeks?") (Sands et al., 2010), combined with two simple attention tests (reciting the days of the week and months of the year backwards (O'Regan et al., 2014, Hall et al., 2012)). If any of these tests were pathological, if the patient was drowsy, or if the nurse and/or the treating physician for other reasons suspected delirium, ascertainment of delirium or subsyndromal delirium was performed.

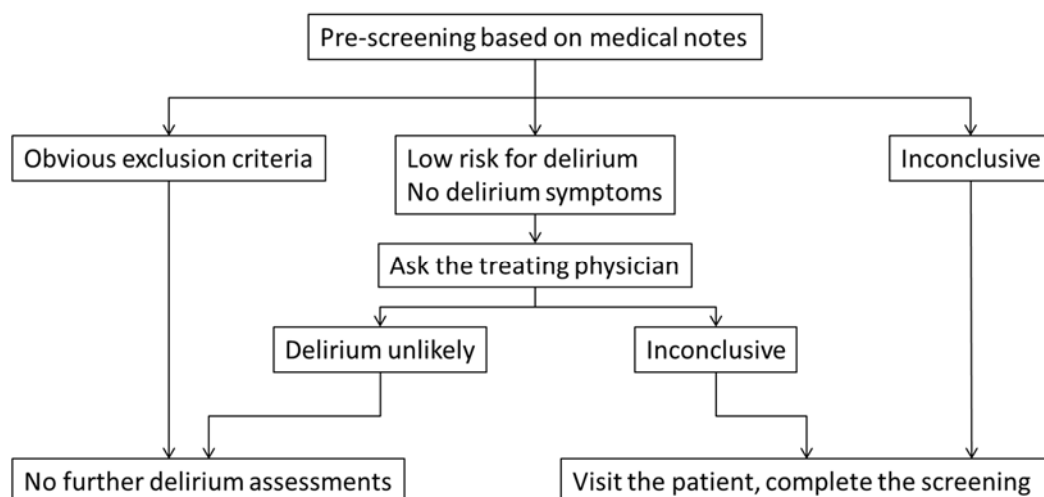
All patients (above 65 years) admitted to the study wards went through a simple screening process and got a screening number (figure 5). This was done on a daily basis, except in the weekends and during the summer holiday. From January 2015, all patients >65 years in the acute medical observation unit and the acute geriatric ward were routinely screened, but occasionally also patients in the stroke unit (as many geriatric patients are admitted there without an acute cerebrovascular event), and in the ward for general internal medicine.

We were two delirium researchers (KRH, BEN) who read the case notes for all the newly admitted patients. All notes from nurses and physicians from the hospital admission until the day of screening were reviewed; admission notes, daily (and night shifts) nursing notes, and progress notes. In the reading of the charts, we paid especially attention to “trigger words and phrases” like:

Mental status change/altered mental status, signs of fluctuations (changes in the description of the patients mental status in the medical notes), delirium or delirious, signs of inattention (the patients seems easy to distract, does not cooperate, do not follow instructions, cannot explain his/her own wishes, failed on attention tests performed at admittance), the patient is alert and oriented, hallucination, hallucinating, confuse, confusion, disoriented, unresponsive, somnolent, drowsy, low Glasgow Coma Scale (GCS) at admittance, agitated, restless, paranoid, delusions.

- KRH and/or BEN identified all new patients and did an initial evaluation based on readings of the medical records.
- If the patient was considered at low risk for delirium, and no symptoms associated with delirium were described in the medical notes or nurse notes, the investigators asked the treating staff if they suspected delirium. If negative, no further assessments were done.
- Likewise, if the medical record revealed obvious exclusion criteria (impaired kidney function, pulmonary oedema, etc.); no further delirium assessments were performed.
- In all eligible patients where the initial case note based screening or information from the staff was inconclusive, the investigators visited the patients and performed a delirium screening as presented in table 7.

Figure 5. The screening process in LUCID



7.1.4 Diagnosis of delirium and subsyndromal delirium

Table 8. Diagnostic algorithm for DSM-5 delirium

DSM-5 criteria	Tests to be performed or information needed			DSM-5 criteria fulfilled?	
				YES	NO
A. Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).	Evaluation	TEST	Cut off (definition of inattention)		
	Daily	Digit span forward	less than 5 forward		
	Daily	Digit span backward	less than 3 backwards		
	Daily	SAVEAHAART*	2 or more errors		
	Initial diagnosis only	Days of the week in reverse order	any error		
	Initial diagnosis only	Months of the year in reverse order	unable to reach July		
	Initial diagnosis only	Count backwards from 20 to 1	any error		
B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.	Observation (by the examiner): Distractibility. Comprehension. Tendency to lose the tread of conversation. The “DelApp” [level of arousal test followed by counting of serially-presented lights. Cut-off 7/8 out of 10]				
	Informant history from patient’s carers and nursing staff Questions to carer/ nursing staff or derived from clinical notes: Has there been a sudden change in the patient’s mental state? Does the patient seem to be better at any period in the day compared to other times? Has the level of consciousness been altered (drowsy/ not interacting or agitated)? Sleep-wake cycle disturbances?				
	C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).				
	Questions to the patient: Orientation to time, place and person Recall (3 words) Why are you in hospital? Will a stone float in water? Are there fish in the sea? (any error = disorganised thinking) Questions to carer/ nursing staff or derived from clinical notes: Has there been any...: Perceptual disturbances? Sleep-wake cycle disturbances? Memory disturbances? Psychotic symptoms? Psychomotor abnormalities?				
	D. The disturbances in criteria A and C are not explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.				
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e., because of a drug of abuse or to a medication), or exposure to a toxin or is because of multiple etiologies.	Information from history/chart/clinical assessment				
	Information from history/chart/ clinical assessment				
Delirium based on the tests and information above?	All DSM-5 criteria fulfilled			Yes <input type="checkbox"/>	No <input type="checkbox"/>
Subsyndromal delirium based on the tests and information above?	Defined as evidence of change, in addition to any one of these: (a) altered arousal, (b) attentional deficits, (c) other cognitive change, (d) delusions or hallucinations. Criteria D and E must be met.			Yes <input type="checkbox"/>	No <input type="checkbox"/>

* SAVEAHAART is an attention test, from the CAM-ICU (Ely et al., 2001). The patient is asked to squeeze on the letter “A” as the rater recites a series of 10 letters “S-A-V-E-A-H-A-R-T”.

The diagnosis of delirium in LUCID was made by the study physicians (KRH, BEN) according to DSM-5 criteria by using a standardized procedure (Table 8). This procedure was made as a part of the preparations of LUCID and is published (Paper IV). Delirium was diagnosed similarly also in the HUT-study (paper III). In LUCID, daily delirium assessments (also during weekends) were made of all included patients.

Acute changes in the patient's mental status as well as fluctuation of any disturbance was ascertained through informant history from nursing staff and carers and also derived from clinical notes. Assessment of additional mental status disturbances was performed by asking the patient a list of pre-defined questions in addition to information derived from nursing staff and clinical notes.

The different scales and tests used in the delirium assessments were:

- The Richmond Agitation and Sedation Scale (RASS) (Chester et al., 2012, Sessler et al., 2002) for assessing the level of arousal. An abnormal modified RASS score (-1 or 1 or greater) is highly associated with delirium (Chester et al., 2012, Morandi et al., 2016, Tieges et al., 2013). Scores of -1 or 1 or greater were 93% specific to delirium. Scores of -2 or 2 or greater were more than 99% specific to delirium (Han et al., 2015).
- The Observational Scale of Level of Arousal (OSLA) for assessing the level of arousal (Tieges et al., 2013). The OSLA-form is completed after having seen the patient, and takes little time (approximately one minute). Assessment is based on observations of the patient and does not require him/her to be able to respond verbally. The scale covers four clinical areas: eye opening, eye contact, posture and movement. Higher scores indicate an abnormal level of consciousness. The total score (0 – 15) is calculated by adding together points from each category. An OSLA cut-off score of 3/4 has a sensitivity of 0.87 and specificity of discriminating delirium from no delirium. This scale was translated into Norwegian as a part of the preparations for LUCID (Neerland et al., 2014).
- These tests were used for assessment of attention:
 - Digit span forward and backward, from Memorial Delirium Assessment Scale (MDAS) (Breitbart et al., 1997)
 - SAVEAHAART, from the CAM-ICU (Ely et al., 2001)
 - Days of the week in reverse order (Hall et al., 2012)
 - Months of the year in reverse order (O'Regan et al., 2014)
 - Count backwards from 20 to 1 (Hall et al., 2012)
- A smartphone (Android) software application, the "DelApp" (Tieges et al., 2015), was used in a few patients. The DelApp incorporates an initial test of level of arousal followed by a test of attention.

All these assessments were used in combination in relation to the DSM-5 criteria. The objective indicators were supplemented by the assessor's judgement regarding subjective features and a final diagnosis was made.

Subsyndromal delirium was defined as evidence of change, in addition to any one of these: (a) altered arousal, (b) attentional deficits, (c) other cognitive change, (d) delusions or hallucinations. DSM-5 criteria D and E must be met.

Delirium status according to the Confusion Assessment Method (CAM) (Inouye et al., 1990) was also registered daily.

The severity of delirium was assessed for all included patients with the Memorial Delirium Assessment Scale (MDAS) (Breitbart et al., 1997), based on the tests and information described above. MDAS is a continuous scale and has a range of sum score 0-30, in which 0 means no delirium symptoms. MDAS point 1-6 was scored based on how the patient was during the interview. MDAS point 7-10 was scored based on how the patient had been since the last MDAS was measured or (if it is the first evaluation or it has been > 24 hours since the last MDAS) the last 24 hours.

7.1.4.1 Inter-rater reliability analyses

In LUCID, all delirium assessments were performed by one of the two study physicians (KRH and BEN).

KRH and BEN assessed 20 patients for interrater reliability analyses, to determine consistency among the raters:

- When we used DSM-5 to distinguish between patients with delirium and no delirium, the Kappa measure of agreement value was 0.83. This represents very good agreement.
- When we used CAM to distinguish between patients with delirium and no delirium, the Kappa measure of agreement value was 0.83. This represents very good agreement.
- When we used OSLA dichotomised with a cut off 3/4 to distinguish between patients with delirium and no delirium, the Kappa measure of agreement value was 0.69. This represents good agreement.
- When we used MDAS to assess the severity of delirium, a two-way mixed effect model, assuming no interaction effect, showed an intraclass correlation (ICC) value of 0.97 (95% CI 0.85-0.99).
- When we used OSLA to assess the level of arousal, a two-way mixed effect model, assuming no interaction effect, showed an ICC value of 0.97 (95% CI 0.93-0.99).

The ICC is very high for both OSLA and MDAS. The explanations for this high ICC are probably that the investigators assessed the patients together. One investigator did the examination and talked to the patients, while the other was only observing. The ratings based on the examination were, however, done independently. The investigators also routinely assessed other patients for delirium together.

7.2 Clonidine intervention

7.2.1 Production and storage of the study drug

The study drug was produced and labelled by Kragerø tablettproduksjon A/S. They used Catapresan tablets, 25 µg, and encapsulated 3 tablets together in one capsule, produced by CAPSUGEL. The capsules containing active medication and placebo looked identical. Each capsule contained either 75 µg Catapresan (clonidine hydrochloride) or 75 µg (3 tablets á 25 µg) placebo.

The study drug was stored in a separate box in a locked room (with a maximum temperature of 25°C) at the acute geriatric ward, where only authorized staff had admittance. The drug had a label permanently affixed to the outside of the box and was labelled according to Good Clinical Practice (GCP) and local regulations.

7.2.2 Dosage plan and administration

The capsule containing clonidine or placebo was administered orally. An initial stepwise loading regimen at day 1 was followed by a lower maintenance dose administered twice daily from day 2. The first dose was given within 48 hours of the diagnosis of delirium/subsyndromal delirium. For practical reasons we included and started medication at daytime. The study drug was prescribed by the investigator (BEN or KRH), and was delivered by ward nurses who signed the standard hospital form as well as a separate form including any medication not swallowed by the patient (for any reason).

The dosage plan for clonidine was:

Day 1/ loading doses: 75 µg every 3rd hour until maximum 4 doses, (e.g.: at 2, 5, 8 and 11 p.m.)

Systolic BP had to be >120 mmHg before the first loading dose. If systolic BP was < 100 mmHg, HR < 50 beats/min or RASS was -3 or less before any of the subsequent loading doses, no more study medication was given until the planned maintenance dose the next morning.

Day 2-7/ maintenance doses: 75 µg BID, at 8-9 a.m. and 8-9 p.m.

If systolic BP was <100 mmHg, HR < 50 beats/min or RASS was -3 or less just before a planned dose, no study medication was given until the next planned dose 12 hours later. If RASS was -2, the treating physician had to assess if study medication would be given or not.

Duration of therapy

The drug was given until the participant was free of all delirium symptoms (by DSM-5 criteria) for 2 subsequent days, or after a maximum treatment of 7 days, or until 24 hours before planned discharge. Thus, we could observe the patients closely for 24 hours after the last intake of the drug.

Patients could also discontinue protocol therapy in the following instances:

- Intercurrent illness which would, in the judgment of the investigator or treating physician, effect patient safety, the ability to deliver treatment or the primary study endpoints.
- Request by patient.
- A pause of >3 following dosages (maintenance dosages) would cause patient discontinuation.

7.3 Monitoring and safety in LUCID

BP and pulse were monitored 3 hours after each loading dose (day 1) and then just before every dose thereafter (2 times/day). If signs of significant hypotension (BP < 100mmHg) or bradycardia (heart rate < 50 beats/min), no study medication was given and further monitoring or treatment was considered individually.

Drowsiness was evaluated daily by KRH or BEN (or by the treating physician during weekends) with RASS to consider further treatment. Nurses always considered if the patient was adequately awake

to be able to take the next dose. Electrocardiogram (ECG), creatinine, blood-glucose and a clinical assessment of hydration status was performed daily. However, if the heart rate was stable during the first days, there were no signs of arrhythmia or AV-block, and the patient was clinically stable, some ECGs were omitted. Orthostatic BP was performed during the hospital stay at day 5, 6 or 7 approximately at 11:00 a.m. (approximately 3 hours after administration of study medication).

7.4 Measurements and questionnaires

An overview of the assessments and the timing of assessments in the different patient samples are presented in table 9. The measurements and questionnaires used in sample 4 and 5 are described more detailed here. The delirium screening methods and delirium diagnosis is described in chapter 7.1.3 and 7.1.4.

Table 9. Overview of methods used for assessments of cognition and level of function in the five study samples (described in section 6.1 to 6.5)										
Domain	Tests	Hospital stay					Follow-up			
Study sample		S1	S2	S3	S4	S5	S1	S2	S3	S5
Delirium	CAM	•	•	•	•	•		•	•	•
	MDAS	•	•		•	•				•
	DRS-R98			•					•	
	Edinburgh Delirium Test Box 1			•					•	
	RASS			•		•				?
	OSLA			•	•	•				•
	DSM-5 based diagnosis				•	•				•
Cognition	IQCODE	•	•	•	•	•	•	•		•
	CDR		•		•	•		•		•
	MMSE	•		•	•	•	•	•	•	•
	Clock drawing test	•					•	•		•
	CERAD 10 word test	•					•	•		•
	Trail Making test A and B									•
Function	Barthel ADL Index	•	•		•	•	•	•		•
	Katz ADL Scale			•					•	
	Nottingham Extended ADL Index	•	•		•	•	•	•		•
	Depression		•		•	•		•		•
Clinical data	Geriatric Depression Scale								•	
	ASA score	•	•	•	•					
	APACHE II	•	•	•	•	•				
	ECG	•	•	•	•	•				
	Weight, height	•	•		•	•		•		
	Charlson Comorbidity Index	•	•	•						
	CIRS				•	•				
	Medication	•	•	•	•	•	•	•	•	•
	Surgical and anaesthesiological procedures	•	•	•						
	Hemodynamic data	•	•		•	•				
	Physical function	•	•			•		•		•
	Biological material	•	•	•		•		•	•	
	CSF		•	•						
CAM = Confusion Assessment Method; MDAS = Memorial Delirium Assessment Scale; DRS-R98 = Delirium Rating Scale Revised-98; RASS = Richmond Agitation Sedation Scale; OSLA = Observational Scale of Level of Arousal; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5 th edition; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; CDR = Clinical Dementia Rating scale; MMSE = Mini Mental State Examination; CERAD = The Consortium Establish a Registry for Alzheimer's Disease; ADL = Activities of Daily Living; ASA = American Society of Anesthesiologists; APACHE = Acute Physiology and Chronic Health Evaluation; ECG = Electrocardiogram; CIRS = Cumulative Illness Rating Scale; CSF = Cerebrospinal Fluid.										

Sample 1 (S1): Juliebø/Krogseth. Follow-up after 6 months

Sample 2 (S2): Watne. Follow-up after 4 (not used in this thesis) and 12 months

Sample 3 (S3): Hall. Follow-up (not used in this thesis) after 1,6 and 12 months

Sample 4 (S4): Neerland, n=14

Sample 5 (S5): Neerland, Hov, n=20. Follow-up after 4 months

7.4.1 Cognition and functional level

Cognitive function: Proxies provided information regarding changes in cognitive function over a 10-year period, using the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-SF) (Jorm, 1994). This is the most commonly used proxy-based scale for cognitive decline, and is shown to be highly concordant with a criterion based diagnosis of dementia (Jorm, 1994, Jorm, 2004, Jackson et al., 2016a, Harrison et al., 2015). The scale consists of 16 items, rated 1 to 5, where higher scores indicate a higher degree of cognitive impairment. A mean is derived from these 16 items (range 1-5). A score of 5 means much worse cognitive function the last 10 years. Different cut-offs have been suggested, and a cut-off ≥ 3.44 was used in sample 1-3. However, a recently published paper suggested a cut-off >3.82 to detect dementia in hospitalised patients with delirium (Jackson et al., 2016a). This cut-off is used in paper III.

The Clinical Dementia Rating scale (CDR) (Hughes et al., 1982) is a proxy-based scale for severity of dementia that is able to detect differences also between patients with severe dementia. This scale consists of six questions, each rated 0-3, adding up to a sum score of 0-18 ("sum of boxes"). The scale is frequently used in dementia treatment trials, and is shown to be valid and reliable. CDR is based on information from the best available sources (combining information from both proxies and the patient).

Most patients were tested with the Mini Mental State Evaluation (MMSE) (Folstein et al., 1975) during the acute hospital stay and at follow-up. The MMSE is a 30-item questionnaire screening test for cognitive impairment.

For patients included in sample S1 and S2 (paper II), a consensus diagnosis were made, both at baseline and at follow-up, by an experienced geriatrician (Torgeir Bruun Wyller) and an experienced specialist in old age psychiatry (Knut Engedal). Based on all information available, they assessed each patient individually and decided whether the ICD-10 research criteria for dementia, see table 4, (www.who.int/classifications/icd/en/GRNBOOK.pdf) were present or not. If any disagreement occurred, they discussed the patient until a consensus was reached. The retrospective diagnosis of pre-fracture dementia at baseline was based on:

- Information from medical records (clinical history, previous diagnosis, test results)
- IQCODE-SF
- Barthel Activities of Daily Living (ADL) Index (Mahoney and Barthel, 1965) and Nottingham Extended ADL Index (NEADL) scores (Lincoln and Gladman, 1992)
- Mini Mental State Examination (MMSE)
- The Clock Drawing Test (Shulman, 2000)
- Test results obtained during the acute stay were only used for dementia diagnosis purposes if the patient did not develop delirium in the acute phase.

The diagnosis of new onset dementia at follow-up was based on:

- The cognitive tests from the home-visit:
 - MMSE
 - The Clock drawing test
 - CERAD 10 word memory task (Morris et al., 1989)
 - The Digit Span Task (by WAIS) (Wechsler D, 2003)
- Barthel ADL Index and NEADL scores
- Caregiver's information regarding cognitive and psychiatric changes after the fracture

- The assessors at follow-up were blinded to delirium status during hospitalisation.

Activities of daily living (ADL): The Barthel ADL Index (Mahoney and Barthel, 1965) is a ten items index of primary activities of daily living (eating, grooming, toileting etc.), adding up to a sum score ranging from 0 to 20. A score less than 20 indicates impairment in basic ADL. The Barthel Index is sensitive to differences among persons with severe or moderate disabilities, but has a profound ceiling effect. In sample 3 (Edinburgh), the Katz ADL was used (Katz et al., 1963).

The Nottingham Extended ADL Index (NEADL) (Lincoln and Gladman, 1992) is assessing instrumental ADLs like handling money and using public transportation, adding up to a sum score of maximum 66. Lower scores mean impairment in complex ADL. The NEADL has good sensitivity in the upper part of the functional range, where the Barthel Index functions poorly. In the acute phase, we used both NEADL and Barthel Index retrospectively, and the proxies were asked to describe the functional level two weeks before admission to hospital.

7.4.2 Biomedical data

Diagnoses were collected from previous medical records and from new diagnoses set during the index hospital stay. The Cumulative Illness Rating Scale (CIRS) was calculated (Salvi et al., 2008). The CIRS assesses fourteen organ systems, and co-morbidity in each organ system is scored on a five-point scale ranging from grade 0 (no problem) to grade 4. CIRS is a further development of the Charlson Comorbidity Index (Charlson et al., 1987).

Clinical findings on admission included systolic (SBP) and diastolic blood pressure (DBP), heart rate, body temperature and oxygen saturation, ECG, and routine blood samples (venous). Intraoperative BP values (paper II) were extracted from the perioperative anaesthesia chart (both electronic and paper records). Artefacts were excluded based on a clinical judgement. Postoperative BP measurements were recorded once 4 hours after surgery.

The American Society of Anesthesiologists (ASA) score (Anesthesiologists, 1963) was collected from the anaesthesiology records or assessed by BEN (sample IV). The Acute Physiology and Chronic Health Evaluation II (APACHE II) score is a measure of physiological disturbance, and was calculated using a version without information on arterial blood gases and haematocrit values (Knaus et al., 1985).

Hand-grip strength was examined by hand-dynamometry. In LUCID, this was done just before discharge and at follow-up.

Medication used at admission and at discharge, as well as use of daily medication during hospital stay was registered. Height was measured using a metric ruler, and an electronic weight was used. Body Mass Index and body surface (paper III) was calculated.

7.5 Sample collection, sample handling and laboratory procedures

7.5.1 Blood and cerebrospinal fluid (CSF)

CSF (sample 2 and 3) was collected at the onset of anaesthesia. Blood was collected preoperatively using venous puncture. After sampling, blood tubes were kept for 30 minutes at room temperature for clotting before being centrifuged. Serum aliquots were stored at -80°C in polypropylene tubes.

Up to 4 mL of CSF was collected in polypropylene tubules just before injection of the spinal anaesthetic. The CSF was centrifuged shortly after collection, and the supernatant was stored in aliquots at -80°C .

Serum and CSF CRP levels were determined using Enzyme-linked immunosorbent assay (ELISA) (DRG Instruments, Marburg Germany). Serum and CSF IL-6 and sIL-6R levels were measured using ELISA (R&D Systems Europe, Abingdon, Oxon, UK). The same operator (blinded to clinical data) analysed all CSF and serum samples in Oslo in May 2011 using the same assay lot numbers during the laboratory sequences. The interassay coefficients of variation in the laboratory were less than 5% for CRP, 36% for IL-6, and 10.5% for sIL-6R.

7.5.2 Blood for analysis of clonidine

Venous puncture for collection of plasma were scheduled 3 hours after each drug intake on day 1, just before drug intake (between 8am and 9am on day 2 and day 5, 6 or 7) and 3 hours after intake at day 5, 6 or 7. Heparin tubes (4ml) with blood was collected by venous puncture and centrifuged (2000G) for 10 minutes and two aliquots of at least 250 μl were stored in polypropylene tubes at -80°C pending analyses. Clonidine in plasma was determined by the method of Muller et al (Muller et al., 2007) with minor adjustments as described in (Sulheim et al., 2014).

7.6 Head-up tilt testing

7.6.1 Experimental protocol

The patients were assessed by BEN at their admittance to the acute geriatric ward. Eligible patients were asked to participate in the study. Written and oral information was given by BEN to the patient and to their relatives. Written consent was obtained the next day. An interview with the patients, including cognitive tests, was done a few hours after the HUT by BEN. The patients were assessed for delirium both the day of HUT and the day before by BEN. Demographic and clinical data were collected at inclusion and during the hospital stay, including CIRS, APACHE II, ASA, IQCODE, CDR, Barthel ADL, NEADL, Cornell (Alexopoulos et al., 1988), BMI, venous blood samples. (See previous chapters for details about the scales and assessment tools).

Table 10. Selection criteria for participation in the head-up tilt testing study

Inclusion criteria	Acutely admitted with an infection Signed informed consent from patient or relatives, and expected cooperation
Exclusion criteria	Moribund (as assessed by the treating physician) Atrial fibrillation Pacemaker Polyneuropathy Ongoing treatment with beta blockers, calcium antagonists or acetylcholinesterase inhibitors

7.6.1.1 Head-up tilt-testing

All HUTs were performed in the morning, between 9 and 10 a.m., in a quiet room with comfortable temperature and dimmed lighting. The patients fasted overnight, but were allowed to drink (water, juice, milk) and to eat their medicines.

Figure 6. Head-up tilt-test, 15 degrees tilt



We designed a modified procedure for HUT, as the patients were too frail to be moved to a separate tilt-table for testing. The patients could stay in their regular hospital bed during the HUT. These could be tilted to 15 degrees (see figure 6). The patients were laying supine, attached to a Task Force Monitor (TFM) (CNSystems Medizintechnik, Graz, Austria), a combined hardware and software device for non-invasive beat-to-beat recordings of cardiovascular variables. Baseline registrations were done for 5 minutes when the patients rested horizontally, before they were tilted head-up to 15 degrees for 10 minutes. The subjects were asked to relax and remain silent except for comments about discomfort. The chosen low tilt angle (15 degrees) challenges the cardiovascular system, but provides less discomfort than larger angles, and was the largest angle possible using the regular hospital beds.

7.6.1.2 Recordings

4 electrodes were placed for ECG recording, and 3 band electrodes were placed on the neck and upper abdomen for impedance cardiography (ICG). ICG is a method in which a small electrical potential is applied between the band electrodes. The method gives a continuous recording of the transthoracic impedance (dZ/dt) (Fortin et al., 2006, Gratze et al., 1998). Continuous recording of arterial blood pressure was obtained using a non-invasive technique/photo plethysmography on the right second and middle finger (see figure 7). This method correlates well with invasive blood pressure measurements (Parati et al., 1989). The recorded value was calibrated against conventional oscillometric measurement of arterial blood pressure.

Figure 7. Non-invasive arterial blood pressure measurement. This is *not* a study participant. According to our protocol, the right hand was placed on the chest (figure 6).



During the HUT, all recordings were transferred on-line to the TFM software for real-time data acquisition.

The primary variables measured beat-to-beat by the TFM are:

- From the ECG: Heart rate (HR)
- From the ICG : Stroke volume (SV)
- From the non-invasive technique (photo plethysmography): Arterial blood pressure (SBP, DBP, MAP)

From these variables, other conventional cardiovascular beat-to-beat variables were calculated:

- Cardiac output (CO) = SV x HR
- Total peripheral resistance (TPR) = MAP/CO

All variables based upon volume measurements (CO, SV, TPR, and EDV) were normalized according to body surface area (BSA) (Gehan and George, 1970).

$$BSA (m^2) = 0.0235 \times \text{Height (cm)} + 0.42246 \times \text{Weight (kg)} + 0.51456$$

7.6.2 Heart rate variability

Continuous cardiovascular variables, such as blood pressure or heart rate, can be subjected to variability analyses. This can provide additional information about the autonomic cardiovascular control compared to conventional variables alone. Analyses of sympathetic and vagal (parasympathetic) activity are derived from heart rate and blood pressure variability. We have not assessed blood pressure variability in this study.

Heart rate variability describes the variations of instantaneous RR-intervals (Malik, 1996). Fluctuations in the interval between successive heartbeats are primarily modulated by the autonomic nervous system (ANS) inputs to the sinus node. HRV analysis can thus be seen as a non-invasive method to study cardiac ANS activity.

Variations in heart rate can be assessed by different methods:

1) Using the *time domain* measure, the extent of variability within a recording of a certain length is expressed using common statistical terms, such as mean and standard deviation. Each R deflection in the QRS complex is detected, and RR-intervals are determined. The most commonly used measures derived from RR intervals are:

- SDNN: Standard deviation of all RR-intervals
- NN50: Number of pairs of adjacent RR-intervals differing by more than 50 ms
- pNN50: NN50 count divided by the total number of all RR intervals (or: the percentage of consecutive RR-intervals differing by more than 50 ms)
- RMSSD: The square root of the mean of the sum of the squares of differences between adjacent RR intervals

2) Analyses of HRV might also be performed in the *frequency domain* and requires more complex mathematical procedures. The most common is the non-parametric method called Fast Fourier Transformation (Bianchi et al., 1997). The extent of variability is expressed as the power of different frequencies. The spectral analysis of short term (2-5 minutes) recordings distinguishes the main spectral components from the recording: Very low frequency (VLF), low frequency (LF) and high frequency (HF) components. The distribution of the power and the frequency of LF and HF are not constant, but might vary in relation to changes in autonomic modulations of the heart period (Malik, 1996). The TFM provides the power spectral analysis for HRV automatically. Total power is considered to be the area under the power spectral curve (PSD). Three frequency ranges (spectral bands) are defined by convention (Malik, 1996):

- Very low frequency (VLF) : <0.04 Hz
- Low frequency (LF): 0.04-0.15 Hz
- High Frequency (HF): 0.15-0.40 Hz
- The power spectral density (PSD) is the power distribution across frequencies, representing total variability

Both HF and LF can be expressed in normalized units (nu): $HF_{nu} = HF / (\text{total power} - VLF) \times 100$. $LF_{nu} = LF / (\text{total power} - VLF) \times 100$

The RR-interval power spectral density in the LF-band might be considered a measure of activity of both the sympathetic and the parasympathetic system (Malik, 1996). The density in the HF-band is considered as a measure of parasympathetic activity. The LF/HF-ratio is thus regarded as a reflection of the sympathicovagal balance in the modulation of HR. VLF is not used in short time frequency analysis.

Table 11. Approximate correspondence of time domain and frequency domain methods

Time domain variable	Approximate frequency domain correlate
SDNN	Total power
pNN50	HF
RMSSD	HF

7.6.3 Data analysis of the HUT-recordings

The plots of the beat-to-beat recordings for each patient were scrutinized. Two time series of 4 minutes were selected from each patient for analyses; 270-30 seconds prior to the 15° head-up-tilt (rest) and 120-360 seconds after the tilt (HUT). Delta-tilt values were calculated (HUT - rest). Ectopic beats, obvious artefacts due to instrumental failure, and their corresponding blood pressure values were manually removed and replaced by linear interpolation. We then computed the median of all cardiovascular variables in all time periods and transferred the values to the statistical software (SPSS) for further statistical analyses.

All calculations of HRV in time domain were manually performed in Excel. The RR-intervals were calculated from the ECG-recorded HR (1/HR) and further calculations of SDNN, pNN50 and RMSSD for the defined time series were performed.

7.7 Statistics

All statistical analyses were performed using SPSS Statistics version 21-24 (IBM, Armonk NY).

7.7.1 Comparing groups (paper I-III and V)

Student's t-tests (normally distributed data) or Mann-Whitney U-tests (skewed data) were used to compare independent continuous variables. Categorical variables were analysed using Chi-square tests. Wilcoxon signed ranks test was used for comparisons of paired observations (skewed data). For all analyses a p-value of <0.05 was considered indicative of statistical significance.

7.7.2 Regression analyses (paper II)

Multiple logistic regression analysis explores the effect of different independent variables (both categorical and continuous) on one categorical variable, often binary. In paper II, logistic regression was used to assess what independent variables could predict the incidence of a) postoperative delirium, and b) new-onset dementia at follow-up.

Due to a limited sample size, the statistical power was too small to include all possible candidate variables into the model. Variables with p-values ≤ 0.10 in univariate analyses were chosen for the multivariate logistic regression models. These were "candidate variables". We then followed a stepwise procedure for variable selection:

- First, intermediate models were created, based on a clinically reasonable division of the candidate variables into background variables (e.g. age, level of functioning, etc.), variables related to preoperative conditions (e.g. time from admission to surgery, severity of illness/ASA score), as well as peroperative and postoperative variables.
- We explored the potential risk factors in each of these categories separately in the first intermediate models, and then merged the significant variables (p-values <0.05) from each of these categories in the final multivariate model.

- Both forward and backward stepping procedures for variable selection were used.
- Continuous variables were categorised into quartiles or quintiles to check for linearity in their relation to the outcome variable. If their relationship to the outcome was not homogenous through their entire range, they were recoded into ordinal variables (cut points based on quartiles or quintiles) or dichotomised as appropriate based on the preliminary analyses.
- We assessed for confounders, and investigated multicollinearity using a correlation matrix and by exploring the variance inflation factor (VIF). If we identified a correlation coefficient above 0.6, one of the variables was omitted.

Information can be lost in the process of categorizing variables. However, if the relationship between a continuous explanatory variable and the odds of the outcome at stake is far from linear, forcing the continuous explanatory variable into the model may give misleading results. As recommended by Hosmer & Lemeshow (*Applied logistic regression, 2nd edition. Hoboken: John Wiley & Sons Inc. 2000*), we explored the relationship between each explanatory variable and the odds for the outcome, and categorized or dichotomized the explanatory variables as appropriate. Finally, we also did sensitivity analyses using continuous variables instead of the dichotomized variables.

7.7.3 Primary and secondary endpoints in the RCT (paper IV)

Choice of primary endpoint and statistical methods in treatment studies for delirium is not straightforward. Studies of delirium often have small sample sizes and sample attrition. The natural trajectory of delirium varies greatly and the course is by definition fluctuating. It is also difficult to decide what a clinically relevant treatment effect is. Standard statistical analysis looking at days-to-resolution alone or maximum severity alone, would make it difficult to achieve sufficiently high power. These entities might also not represent the complex condition of delirium. Accordingly, we have chosen a more "global" approach, looking at the delirium trajectory with mixed linear models. This makes it possible to use all available data - even if some data should be missing (Farewell et al., 2012). Using longitudinal trajectories as the main outcome would give greater power than end-of-trial analyses (Tahir et al., 2012, Adamis, 2009). These methods will increase the power of the study.

The primary endpoint in LUCID is the repeated measurements of MDAS over time. MDAS is a continuous scale, described in more detail in chapter 7.1.4. Differences in the MDAS trajectories between the treatment groups will be analysed by a mixed linear model.

In addition we decided, as a secondary endpoint, to compare the time to resolution of delirium as measured by DSM-5. The Kaplan Meier method and the log rank test will be applied. In addition a Cox proportional hazards model will be applied to estimate hazard ratios. The additional different secondary endpoints will be analysed by t-tests or Mann-Whitney tests when variables are continuous and by chi-square tests when variables are categorical. Patient survival will be compared between groups by the log rank test and Cox proportional hazards model.

For the comparison of the MDAS trajectories no adjustment for multiplicity will be applied. If a statistically significant difference between the MDAS trajectories is demonstrated, analyses of secondary endpoints will be performed without any formal adjustment for multiplicity. If any conclusion on efficacy is to be drawn based on a secondary endpoint only, a simple Bonferroni adjustment (dividing the 5% level with the actual number of tests performed) will be applied.

Table 12. List of endpoints and measurements for efficacy assessment in LUCID

Endpoint	Measurements for efficacy assessment
Primary	
Delirium trajectory	MDAS
Secondary (also with subanalyses for subsyndromal delirium and hypoactive/hyperactive/mixed delirium)	
Time-to-first delirium resolution	DSM-5
Incidence of “full-scale” delirium	DSM-5
Severity of delirium	MDAS, OSLA
Delirium subtype	MDAS, OSLA, DelApp
Use of “rescue medication”/ additional drugs (as other sedatives, analgesics and antipsychotics)	Registration of use of all medication
Length of hospital stay	Registrations
Patient distress	Checklist of Nonverbal Pain Indicators
Cognitive function in follow-up after 4 months	MMSE-NR, Clock drawing test, Ten-words memory test, Trial making test A and B IQCODE, CDR
Independence in follow-up after 4 months	Barthel ADL, NEADL
Pharmacokinetic response to clonidine	Serum drug concentrations
Pharmacodynamic response to clonidine	BP, HR, ECG, RASS, OSLA, symptoms of bradycardia, orthostatic hypotension or other side-effects
Biomarkers	Blood samples
Institutionalization	Registrations
Survival	Registrations
Safety	
Side effects of clonidine/ in-hospital complications	BP, HR, ECG, sedation (RASS, OSLA), and any symptoms of bradycardia, orthostatic hypotension or other side-effects

7.7.4 Determination of sample size and power calculations (paper IV)

Based on the expected number of patients fulfilling the inclusion criteria within 36 months a sample size of $n = 100$ was chosen. However, it was decided that the first 20 patients would serve some piloting purposes, both with respect to pharmacokinetics of clonidine, and also to perform a safety review concerning dosage.

It was foreseen that 100 patients was probably too small to achieve a sufficiently high power to detect treatment differences with the use of standard statistical analysis methods. Inclusion of 100 patients would lead to a power of only 71% to detect an absolute treatment difference of 25% in proportion recovered according to DSM-5 (40% vs 65%). Correspondingly, using MDAS at one single point in time as the response measure would lead to approximately 80% power assuming a standard deviation of 9 and a difference in mean MDAS score of 5.

Thus, analysing treatment efficacy at only one point in time would lead to low power. An analysis of repeated measurements reduces random variability and thereby increases power. The primary analysis chosen was therefore a mixed linear model taking all MDAS measurements into account.

The expected efficiency gain with repeated measurements depends primarily on the correlation between measurements from each subject. The expected efficiency gain was difficult to estimate precisely, but assuming a standard deviation of 9 on the MDAS and a correlation between measurements of $r = 0.5$, the power would be around 95% to detect a mean MDAS difference of 5 or a power of 80% to detect a mean difference of 3.5 between groups. Based on estimates of correlation in MDAS over time from other studies (Watne et al., 2014), the efficiency gain was expected to be at least in this order of magnitude.

7.8 Ethical considerations

All studies included in this work have been conducted in accordance with the Declaration of Helsinki, and in accordance with regulations by the Data Protection Authorities.

The RCT (LUCID) is conducted in compliance with Good Clinical Practice (GCP). An authorized Clinical Study Monitor has visited BEN and KRH (investigators) on a regular basis, and checked Case Report Forms, discussed the progress of the study and monitored drug usage and safety.

Informed consent is a well-known challenge in studies of delirium (Holt et al., 2008, Adamis et al., 2010), both due to the nature of delirium itself and due to the fact that people with underlying dementia are most at risk of developing delirium. In delirium studies most patients do *not* have capacity to consent at inclusion. However, it is important to make an individual evaluation. Some patients (e.g., patients without dementia who present with a fluctuating, perhaps subsyndromal delirium) might possibly have this capacity, and it is important not to wrongfully disempower them.

Due to the severe impact of delirium upon health and well-being, it is ethically important that research on this patient group is carried out. If patients considered to lack capacity to consent were excluded, there would be a significant selection bias. The population would be younger, less cognitively impaired and with milder cases of delirium, thus decreasing the generalisability of the study results.

In our studies, we have considered the risks for the patients low and justified compared to the potential harm done by non-generalizable, biased studies or the lack of studies.

In our study group (Oslo Delirium Research Group), we have carefully established routines for inclusion that take care of the dignity and rights of people with reduced capacity to consent. Some important aspects and practicalities used in my work are summarized here:

- Cognitively intact patients could be included on the basis of written, informed consent. We developed a full information leaflet for cognitively intact patients and a simplified and shortened one for patients with somewhat reduced competence. When the latter version was used, a close relative received the full version of the patient information. For patients considered lacking capacity (due to severe delirium and/or dementia), but who willingly took part, we obtained proxy informed consent from a close relative. Consent to remain in the research was obtained if capacity returned.

- Seeking written consent from relatives of those patients who lack capacity was not possible within the timeframe for a delirium study (Watne et al., 2014). Due to the importance of including patients as soon as possible after the diagnosis of delirium is made, the close relatives could give verbal consent (by phone) before randomization (LUCID and Oslo Orthogeriatric Trial) and the written consent was obtained as soon as possible after inclusion.
- In LUCID and the HUT study, the investigator was responsible for giving the patients and their relatives/next-of-kin full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. The information given to the patient was adjusted according to the patients' condition and mental capacity at the time. It was emphasized that the participation was voluntary and that the patient/relative/next-of-kin was allowed to refuse further participation whenever she/he/they wanted. No patients were included if the close relative did not consent. We also needed their cooperation for the proxy information.
- A copy of the patient information and consent was given to the patients/relatives/next-of-kin.
- For the Head-up tilt testing, all participants were thoroughly informed about the content of the experiments both orally and in written form. They were given a certain time after information was given before they were asked (the next morning) if they were willing to participate in the study. The right to withdraw at any time was emphasized. They were asked to report symptoms of discomfort during the HUT.

Ethical approvals:

- Paper I: The study was approved by the Regional Committee for Ethics in Medical Research in Norway (REK s-09169a) and the Scotland A Regional Ethics Committee in the United Kingdom.
- Paper II: Ethical approval for this study was provided by Regional Committee for Ethics in Medical Research in Norway. Cohort 1 (REK s-05075) was approved on 18 April 2005, and Cohort 2 (REK S-09169a) on 25 March 2009.
- Paper III: The HUT-study was approved by the Regional Committee for Ethics in Medical Research in Norway (REK 2011/2498) on 28 February 2012, and by the Data Protection Authorities.
- Paper IV-V: The study of clonidine in delirium (LUCID) has been approved by the Regional Committee for Ethics in Medical Research in Norway (REK: 2013/525) and the Norwegian Medicines Agency. The trial is registered ClinicalTrials.gov (NCT01956604) and in EudraCT (2013-000815-26).

8 Results

In the following sections, main results from the papers I, II, III and V are briefly summarised. For a complete description of the results, please see the respective papers.

8.1 Paper I

CSF samples were available for 151 participants (Oslo, n=99, Edinburgh, n=52). Median age was 84 years. More participants in Oslo than in Edinburgh had pre-fracture cognitive impairment (56% vs 10%) and fewer were independent in ADLs (42% vs 90%). One-third of participants in Oslo lived in nursing homes before their hip fracture. In Edinburgh, such individuals were excluded. More individuals were diagnosed with delirium in Oslo than in Edinburgh (52% vs 39%).

There were no significant differences in serum or CSF CRP, IL-6, or sIL-6R levels between participants with and without delirium. Nor was there any difference in the percentage of samples with detectable CSF CRP levels between the groups.

Biomarker results stratified according to pre-fracture cognitive impairment

In participants without preoperative cognitive impairment (IQCODE score <3.44), those with delirium had significantly higher CSF CRP levels than those without delirium (0.05 µg/mL, interquartile range (IQR) 0.02–0.12 vs 0.01 µg/mL, IQR 0.00–0.06, $p=.01$). This group of participants also more often had detectable CSF CRP levels (80% vs 52%, $p=.01$). No such difference was found in participants with pre-fracture cognitive impairment. Serum CRP was not different according to delirium in participants with or without pre-fracture cognitive impairment, and there was no difference in either stratum between participants with and without delirium in CSF or serum IL-6 or sIL-6R levels.

Subgroup analyses of preoperative versus incident (postoperative) delirium

For secondary analyses, participants were divided into subgroups (preoperative delirium, n=37; incident delirium (Postoperative Days 1–4), n=30; never delirium, n=42). Participants with subsyndromal delirium were excluded from these analyses. In participants without cognitive impairment, the CSF CRP concentration was highest in participants with preoperative delirium. The differences were statistically significant between these three different groups (Kruskal-Wallis test, $p=.02$) and in post hoc Mann-Whitney U-tests with Bonferroni adjustment for multiple comparisons. In participants with cognitive impairment, CSF sIL-6R levels were highest in participants with incident delirium, but this did not reach statistical significance (Kruskal-Wallis test, $p=.06$).

Correlational analyses

In the whole sample, there were significant correlations between CSF and serum CRP ($\rho=0.356$, $p<.001$) and sIL-6R ($\rho=0.473$, $p<.001$) levels. When stratified according to delirium status, these correlations were mostly statistically significant. (The correlation between CSF and serum CRP showed a trend in the expected direction.) No such relationships were found for CSF and serum IL-6.

Table 13. Significant differences in CSF and serum findings between patients with and without delirium

		IQCODE <3.44	IQCODE ≥3.44
CSF	CRP	↑ in delirium	no difference
	IL-6	no diff.	no diff.
	IL-6R	no diff.	no diff.
Serum	CRP	no diff.	no diff.
	IL-6	no diff.	no diff.
	IL-6R	no diff.	no diff.
CSF		↑CRP in preoperative delirium vs incident delirium	↑ IL-6R in incident delirium vs preoperative delirium

8.2 Paper II

In all, 696 patients were included in the study, 364 from Cohort 1 and 332 from Cohort 2. Of the included patients, 536 were assessed for delirium preoperatively; 149 (28%) had preoperative delirium, whereas 387 patients had no preoperative delirium and were eligible for analysis of incident delirium. Preoperative delirium assessments are missing for 127 patients in cohort 1 and 33 patients in cohort 2 because the assessors (study nurses/physician) did not manage to see the patients before the surgery.

Preoperative delirium

Patients with preoperative delirium were significantly older and more functionally impaired, more often had preoperative cognitive impairment, were more often living in an institution and were more likely to have fallen indoors. They presented with more polypharmacy, had higher heart rate and lower peripheral capillary oxygen saturation (SpO₂), were in higher ASA groups and had a longer waiting time from admission to surgery than those without delirium.

Preoperative delirium data are missing for 127 patients in cohort 1 and 33 patients in cohort 2. The reason for the missing data is that the assessors (study nurses/physician) did not manage to assess the patients before surgery. The prevalence of pre-fracture dementia and other baseline characteristics were equal between these groups.

Incident delirium

Of the 387 patients who were free from delirium preoperatively, 124 (32%) developed delirium after surgery (incident delirium). In 29 of the 387 patients, an IQCODE score was missing. They were excluded from further analyses. Among patients with an IQCODE score < 3.44 (i.e. no preoperative cognitive impairment; Table 4), univariate analyses showed that patients with delirium were more likely to have an NEADL score of < 45 points and a BMI of < 20 kg/m², to be in ASA group III or higher, or to receive ≥ 2 blood transfusions. In the final multivariate model, having a BMI of < 20 kg/m², having an NEADL score of < 45 points, being in ASA group ≥ 3, and receiving ≥ 2 blood transfusions were found to be independently associated with incident delirium.

In patients with a preoperative IQCODE score of ≥ 3.44 (i.e. cognitive impairment), those who developed incident delirium more often received benzodiazepine perioperatively.

No significant associations were found between incident delirium and perioperative haemodynamic variables, type or duration of anaesthesia, or the administration of a vasopressor, neither in those with nor without preoperative cognitive impairment.

Table 14. Variables significantly associated with incident delirium in multivariate analyses

IQCODE <3.44	IQCODE ≥ 3.44
NEADL < 45	Receiving benzodiazepines perioperatively
BMI < 20	
ASA ≥ 3	
≥ 2 blood transfusions	

New onset dementia

Of all the patients, 273 were free from pre-fracture dementia, of which 213 were assessed at six (n=106) or 12 (n=107) months postoperatively, and 26 (12%) were diagnosed with incident dementia. In univariate analysis, these patients were significantly older, had lower NEADL scores, were in higher ASA groups, and more often had delirium during their index stay than patients without new-onset dementia. Furthermore, they had significantly higher MAP at admission, as well as postoperatively, and they more often received vasopressor drugs during surgery. They tended to have a greater fall in MAP from admission to the peroperative state, but this difference was not statistically significant.

In the final multivariate model, being more than 82 years old, being in ASA group ≥ 3 , having received a vasopressor during surgery, having higher MAP postoperatively and having suffered from delirium during hospital stay were found to be independently associated with new-onset dementia at follow-up.

Table 15. Variables significantly associated with new-onset dementia in multivariate analyses

Age > 82 years
ASA ≥ 3
Delirium
Received vasopressor peroperatively

8.3 Paper III

Fourteen participants (5 with delirium) were included. Patients with delirium had higher CRP values at the time of HUT (median 174 [range 67-306] mg/L vs 62 [7-191], mg/L p=0.04). They were also older (median 89 [84-91] years vs 86 [74-91] years), had a higher CIRS score (median 14 [7-19] vs 10 [1-17]) and a lower NEADL (median 28 [9-30] vs 52 [13-66]), but these differences were not statistically significant. The percentage of patients with an IQCODE > 3.82 was similar in the delirium group (40%) and in the group without delirium (44%).

Autonomic response to HUT to 15 degrees

During HUT to 15 degrees, HR and BP values were stable. There was a slight, but significant decrease in SI ($p < 0.001$) and an increase in TPRI ($p < 0.001$). Indices indicating increased sympathetic activity (LF-variables and LF/HF-ratio) also increased slightly, but these changes were not significant.

Hemodynamic regulation according to delirium status

HR, BP, SV, CO, TPR and EDV were similar across the two groups at rest, but there was a trend towards stronger increase in systolic BP and HR during HUT in the delirium group. There were also no significant differences between the groups in these conventional cardiovascular variables during HUT. However, there was a trend towards stronger increase in systolic BP and HR during HUT in the delirium group.

Heart rate variability according to delirium status

All HRV indices were higher in the delirium group at rest, but not statistically significant. In particular, there was a tendency in the delirium group to higher values of LFabs ($p = 0.06$), SDNN ($p = 0.06$) and pNN50 ($p = 0.06$). During HUT, the delirious patients had a tendency to higher power spectral density (PSD) ($p = 0.06$), lower LFnu and higher HF nu, and thus a lower LF/HF-ratio than the control group ($p = 0.06$). Delirious patients had a significantly stronger reduction in SDNN from baseline than the controls ($p = 0.01$). Patients with delirium also had a non-significantly stronger reduction in PSD during HUT compared with the non-delirious group.

8.4 Paper IV

This is a protocol paper and does not contain any results.

8.5 Paper V

Of 4282 patients screened, 20 patients fulfilled the selection criteria and were included in LUCID between April 2014 and February 2017 and randomised to either clonidine ($n = 10$) or placebo ($n = 10$). Median age was 86 years (range 66-95), and 13 (65%) were women.

Plasma concentrations

Three hours after the first dose of 75µg clonidine, plasma concentration rose to median 0.35 µg /L (range 0.24-0.40) and before drug administration at day 2 the median trough concentration was 0.70 (0.47-0.96) µg/L. After 4-6 days of clonidine treatment, median trough concentration (C_{null}) was 0.47 (0.36-0.76) µg/L, rising to a level of 0.74 (0.56-0.95) µg/L (C_{max}) three hours after administration of the regular dose of 75 µg clonidine.

Hemodynamic changes during treatment

At day 1, 5 of the 7 patients in the clonidine group that received all 4 loading doses had their BP measured 3 hours after the last dose, and there was a statistically significant drop in SBP from

baseline, $p=0.04$. Further, in all 10 patients in the treatment group there was a non-significant reduction in SBP from median 141 (range 124-190) mmHg at baseline to 135 (81-170) mmHg at day 2, $p=0.06$. There was no significant difference in SBP from baseline to the last SBP during treatment (137 (102-238) mmHg, $p=0.5$). For diastolic blood pressure (DBP) and HR there was a trend towards lower values, both in the morning at day 2 and at last measurement, but this was not statistically significant.

In patients who received clonidine, median SBP fell from baseline to day 2 (median change -16, range [-61 - 40] mmHg), and from baseline to last measurement during treatment (median -10 range [-46 - 98] mmHg), illustrating the trend of a drop in these variables. In the placebo group, SBP remained stable. Both within the clonidine and the placebo group the range for these values were considerable, and there were no statistically significant differences between the two groups, $p=0.17$.

A test for orthostatic hypotension was performed in 11/20 patients. In the clonidine group, 1 of 6 patients had a fall in SBP >20 mmHg, versus 1 of 5 patients in the placebo group. During the whole treatment period, a SBP <100 mmHg was measured 3 times in the clonidine group. SBP was also measured <100 mmHg once in the placebo group. One patient had one measurement of HR 49, all other HR measurements were >50 at all times and no patients had any relevant ECG changes.

One patient had a large drop in SBP from baseline to day 2 (from 142 to 81 mmHg). This patient also had the highest plasma concentration level after the third loading dose ($1.0 \mu\text{g/L}$) and before the drug administration on day 2 ($0.96 \mu\text{g/L}$).

Other important events

On the 5th day of treatment one patient in the clonidine group developed a hypertensive pulmonary oedema (SBP 238 mmHg) and following study protocol, the study drug was halted and a report of a possible Serious Unexpected Serious Adverse Reaction (SUSAR) was filed routinely to The Norwegian Medicines Agency. The patient died 2 weeks later. This was considered not related to the study drug. In the placebo group two patients died during the hospital stay or shortly after discharge.

Missing samples

Twenty-seven of 70 (39%) scheduled blood samples are missing. For the planned sample after loading dose 4, 9 of 10 samples are missing (including 3 where the patients never received the 4th dose). In 2 of the 7 patients that received the 4th loading dose of clonidine, a control BP 3 hours after this last dose was missing.

9 Discussion

9.1 The main results in this thesis

- High CSF levels of CRP may be associated with delirium (paper I).
- Different pathophysiological mechanisms may operate in different patient subgroups, in particular in relation to the presence of prior cognitive impairment (paper I and II).
- Likewise, risk factors for incident delirium in hip-fracture patients seem to differ according to pre-fracture cognitive status (paper II).
- Delirium, high blood pressure values postoperatively, receipt of vasopressor drugs perioperatively and severity of physical illness were found to be independently associated with new-onset dementia after hip fracture (paper II).
- Geriatric patients with delirium might have an altered autonomic cardiovascular control compared to non-delirious patients (Paper III).
- We have published a transparent and detailed description of how to diagnose delirium according to DSM-5 criteria (paper IV).
- Only 20 patients were included in LUCID in almost 3 years (paper V).
- Treatment of geriatric patients with clonidine 75 µg every 3rd hour up to a maximum of 4 doses, and further 75 µg twice daily, gave plasma concentration levels within the expected therapeutic range (paper V).
- This treatment with clonidine resulted in a tendency of lower blood pressure values. With dose adjustments based on measurement of HR and BP, the published protocol seems safe (paper V).

The five papers included in this thesis differ in design, material and methods. The following is a discussion of the main results, followed by some methodological and general considerations.

9.2 Discussion of the main results

9.2.1 Neuroinflammation

The neuroinflammatory hypothesis suggests that inflammatory stimulation in the periphery is signalled across the blood–brain barrier and through other pathways, inducing activation of brain parenchymal cells and expression of proinflammatory cytokines and inflammatory modulators and leading to neurocognitive changes characteristic of delirium (Cunningham and MacLulich, 2012). See also chapter 3.3 about delirium pathophysiology. Neuroinflammation is also involved in chronic neurological disorders such as Alzheimer’s dementia (AD) (Pasqualetti et al., 2015). As most hip-fracture patients with delirium have an underlying cognitive impairment, any measured relationships between inflammatory markers and delirium in this population might be confounded by elevated inflammatory markers in dementia. This is why we decided to stratify the analyses (paper I) according to prior cognitive impairment.

Based on the theory of neuroinflammation as a cause of delirium, in paper I, it was hypothesized that delirium in individuals with hip fracture would be associated with high CSF CRP, IL-6, and sIL-6R levels. We found the expected association between delirium and higher CSF CRP levels, but only in patients

free from pre-fracture cognitive impairment. No significant relationship was found between serum and CSF levels of IL-6 or sIL-6R.

We are not aware of other studies of CSF CRP in patients with delirium, and thus direct comparisons of the results cannot be done. Some previous studies found an association between high *serum* CRP and delirium (table 16) (Macdonald et al., 2007, Burkhart et al., 2010, Zhang et al., 2014). However, studies carried out in individuals with hip fracture found no such association (Westhoff et al., 2013, Lemstra et al., 2008). Some previous studies have found high CSF CRP levels in individuals with chronic neurological disorders, such as MCI (Schuitemaker et al., 2009), and dementia in Parkinson's disease (PD) (Lindqvist et al., 2013).

Some studies report higher *serum* IL-6 levels in participants with delirium (table 17) (Westhoff et al., 2013, de Rooij et al., 2007, Plaschke et al., 2010, Egberts et al., 2015, van den Boogaard et al., 2011), but others have not detected such a difference (Cerejeira et al., 2012, Lemstra et al., 2008, Ritter et al., 2014, Adamis et al., 2009). The conflicting results may be due to the use of different methods for analysing cytokines, different compositions of the cohorts, and pooling of prevalent and incident delirium cases. IL-6 is high in a number of age-associated conditions such as frailty and dementia (Erta et al., 2012). A study of individuals with hip fracture found that, after adjusting for previous cognitive impairment, there was no independent association between IL-6 and delirium (van Munster et al., 2010). Time from insult (e.g., hip fracture, surgery) to sampling may also have differed in previous studies. IL-6 plays a major role in early acute phase reactions, subsequently activating the immune system and inducing CRP production (Scheller et al., 2011).

Only two previous studies have explored the association between *CSF* IL-6 levels and delirium (table 18) (Westhoff et al., 2013, MacLulich et al., 2011). One study reported that participants with postoperative delirium had high preoperative serum IL-6 levels but low CSF IL-6 levels (Westhoff et al., 2013). The authors speculate that high serum IL-6 is an early manifestation of a systemic inflammatory reaction that precedes the neuroinflammatory response, although the finding could also represent preoperative vulnerability due to cognitive decline or frailty (Erta et al., 2012) both associated with high serum IL-6 levels. In participants with MCI or AD, most studies show higher levels or no effect on IL-6 in blood and CSF (Brosseron et al., 2014). Small cohorts with different characteristics and severity of disease might explain conflicting findings. Cytokine profiles may change and IL-6 increase during the course of AD (Brosseron et al., 2014).

Table 16. Studies of serum CRP levels in patients with delirium

Author, year	Cohort	Analysing technique	N total (delirium)	Results
Macdonald 2007	Medical	Routine	90 (37,5%)	↑
Burkhart 2010	Cardiac surgery	Routine	113 (35%)	↑
Zhang 2014	Mixed ICU	Routine/Sandwich ELISA	223 (24%)	↑
Westhoff 2013	Hip-fracture	Multiplex (42 cytokines)	61 (37%)	→
McGrane 2011	ICU	Routine	88 (30%)	→ / ↑
Lemstra 2008	Hip-fracture	Sandwich ELISA	18 del, 50 controls	→
De Rooij 2007	Medical	Multiplex	185 (35%)	→

Table 17. Studies of serum IL-6 levels in patients with delirium

Author, year	Cohort	Analysing technique	N total (delirium)	Results
Westhoff, 2013	Hip-fracture	Multiplex (42 cytokines)	61 (37%)	↑
De Rooij, 2007	Medical, age >65y	Multiplex	185 (35%)	↑ IL-6 above detection limit → actual IL-6 level
Van Munster, 2008	Hip fracture	Multiplex	98 (51%)	↑
Van Munster, 2010	Hip fracture	Multiplex	120 (48%)	↑
MacLulich, 2011	Hip Fracture (UK,Neth)	Multiplex	36 (42%)	↑
Plaschke, 2010	Cardiac surgery	Sandwich ELISA	114 (28%)	↑
Egberts, 2014	Medical >65y	ELISA	86 (27%)	↑
Adamis, 2009	Medical >70y	ELISA	67 (42%)	→
Lemstra, 2008	Hip-fracture	Sandwich ELISA	18 del, 50 controls	→
Ritter, 2014	Mixed ICU	ELISA	78 (40%)	→
Capri, 2014	Hip-fracture (no dementia)	Multiplex & sandwich ELISA	37del, 37controls	↑

Table 18. Studies of CSF IL-6 levels in patients with delirium

Author, year	Cohort	Analysing technique	N total (delirium)	Results
Westhoff, 2013	Hip-fracture	Multiplex	61 (37%)	↓ in p.o delirium
MacLulich, 2011	Hip Fracture (UK, Neth)	Multiplex	36 (42%)	→ (IL-6 detect in 3/36) Not further analysed

To conclude, the direction of change in CSF CRP in our study (and also our findings regarding the other neuroinflammatory markers) is not clearly consistent with the neuroinflammatory hypothesis. The peripheral markers of inflammation were all similar between groups, suggesting a similar peripheral challenge. This could imply, provided that the neuroinflammatory hypothesis of delirium is correct, that the responsiveness of the brain to peripheral inflammatory signals is the most important variable. Available animal studies support this notion, because in a given experiment the peripheral inflammatory stimuli (injections of lipopolysaccharide) have been the same in control and neurodegeneration groups (Cunningham et al., 2005, Cunningham et al., 2009, Murray et al., 2012). The theory states that this peripheral inflammatory signal leads to a neuroinflammatory response in people *with* established cognitive impairment. There might be several reasons for this possible

inconsistency: Somehow, there may be increased signalling from serum to CSF in individuals with delirium but no pre-existing cognitive impairment. This could be due to variable blood–CSF barrier permeability or other factors (e.g., drugs, stress response, cortisol). Previous findings indicate that CRP is synthesized in microglia, and differing cerebral production could account for the different CSF CRP findings. High CSF CRP in individuals with cognitive impairment may indicate more chronic inflammation, whereas the high CRP found in individuals with no cognitive impairment and delirium perhaps constitutes an inflammatory trigger.

The direction of change was as expected for CSF IL-6, with the highest values in individuals with delirium and previous cognitive impairment, although the differences were not statistically significant. IL-6 is one of the markers found in animal studies to be produced by primed microglia (Cunningham et al., 2005). CRP may not be the best representative biomarker for testing the neuroinflammatory hypothesis.

9.2.2 Risk factors for incident delirium and new-onset dementia

Incident delirium

The findings in paper II suggest different predisposing factors for postoperative delirium in patients with and without pre-fracture cognitive impairment. Hip-fracture patients actually suffer from two precipitating insults: first the fracture itself, and then the surgery and anaesthesia. The combination of two stressful events in a vulnerable person with cognitive impairment seems to render most other risk factors for delirium relatively insignificant. This view is supported by our findings of cognitive impairment being a significant risk factor for *preoperative* delirium (table 2 in paper II), and also accords with previous studies (Kalisvaart et al., 2005, Lee et al., 2011).

Among patients without pre-fracture cognitive impairment, low BMI, high ASA group, low extended ADL function, and receipt of ≥ 2 blood transfusions were independent and significant risk factors for incident delirium. These risk factors were not found in patients with pre-fracture cognitive impairment.

Benzodiazepines are known to be associated with an increased risk of delirium (Zaal et al., 2015, Clegg and Young, 2011, Marcantonio et al., 1994). Our findings suggest this risk to be particularly relevant in patients with pre-fracture cognitive impairment. Patients with larger cognitive reserves seem to need stronger physiological aberrations, such as major blood loss, to develop postoperative delirium. Our findings are in line with an earlier study (Lee et al., 2011). The authors reported that in the group without dementia, the physical illness severity (e.g. ASA classification), a low BMI and the need for transfusion of more than 2 units of red blood cells were significant risk factors for incident delirium.

No significant associations were found between incident delirium and perioperative haemodynamic variables.

One hypothesis in delirium pathophysiology is that intraoperative hypotension, leading to inadequate cerebral perfusion, increases the risk of postoperative delirium (see chapter 3.3.2.1). Some previous studies have found that intraoperative hypotension is a predictor of postoperative delirium, (Gustafson et al., 1988, Edlund et al., 2001, Patti et al., 2011, Tognoni et al., 2011) whereas

others have not found such an association (Williams-Russo et al., 1999, Marcantonio et al., 1998, Moller et al., 1998, Hirsch et al., 2015) (see table 19). Most studies on intraoperative hypotension and postoperative delirium examine patients undergoing elective surgery, and several have excluded patients with preoperative dementia, thus the results may not generalize to other populations, like high-risk elderly undergoing hip fracture surgery. Only a few previous studies have included hip fracture patients: Two studies from Sweden found perioperative hypotension to be an independent risk factor for incident delirium (Gustafson et al., 1988, Edlund et al., 2001). A more recent study of 103 hip fracture patients reported that neither severe hypertension nor severe hypotension during anaesthesia were associated with postoperative delirium (Wang et al., 2015). Patients with severe cognitive impairment were excluded in that study, and delirium was only assessed once. Our study (paper II) contributes to the body of data regarding hypotension as a risk factor for delirium, and supports that perioperative hypotension, measured by MAP, does not increase the risk of postoperative delirium in hip fracture patients.

Table 19 Studies on intraoperative hypotension and postoperative delirium

Author, year	N	Population	Results	Comments
Gustafson, 1988	111	Hip fractures	92% of patients with ↓BP periop developed delirium	
Marcantonio, 1998	1341	Elective non-cardiac surgery	Hemodynamic complications not risk factor POD	Hypotension=SBP <2/3 of preop BP or SPB<90mmHg requiring pressor or fluids.
Moller, 1998	1218	Elective non-cardiac surgery	Hypoxia or ↓BP not risk factor postoperative cognitive decline	Excluded frail patients and known preoperative cognitive impairment
Williams-Russo, 1999	235	Elective hip-replacement	↓BP not risk factor POD (9%vs4%, p=0.3)	Randomised MAP 45-55 or 55-70 mmHg. Good cognitive data (preop+4mth).
Edlund, 2001	101	Hip fractures	Perioperative ↓BP a risk factor for incident delirium	
Ansaloni, 2010	351	Elective and emergency surgery	Precipitating factors (periop transfusions, ↓BP) lost significance when adjusted for patient vulnerability	Excluded dementia patients
Patti, 2011	100	Elective colorectal surgery	↓BP = risk factor POD	MAP<60mmHg. Excl MMSE<18, AD
Tognoni, 2011	90	Urologic surgery	↓BP = risk factor POD	
Hori, 2014	491	Cardiac surgery with cardiopulmonary bypass	Not ↓BP, but duration and magnitude of BP above the upper limit of CBF autoregulation associated with POD	Only 9 % with delirium

Wang, 2015	103	Hip-fractures	Severe hyper- or severe hypotension = risk fact POD (day 2)	Excluded preop MMSE<15 or delirium
Hirsch, 2015	594	Major non-cardiac surgery	Large BP fluctuations (especially in SBP), not absolute or relative ↓BP, ass with POD	Excluded if not able to consent
Hori, 2016	110	Cardiac surgery	Excursions above the optimal MAP associated POD	Near-infrared spectroscopy (NIRS)
Yang, 2016	343	Elective abdominal, pulmonary and lumbar surgery	Intraop hypertension and tachycardia ass with POD	Excluded MMSE<23

BP: blood pressure, SBP: systolic BP, MAP: mean arterial pressure, POD: post operative delirium, MMSE: Mini Mental State Examination AD: Alzheimer's disease

New-onset dementia

We found that high age, high ASA score, delirium, postoperative hypertension and the use of vasopressors during surgery are independently associated with new-onset dementia at follow-up.

Our findings of age, severity of acute illness and delirium as risk factors are in line with previous research (Fong et al., 2015, Ballard et al., 2011, Saczynski et al., 2012, Annane and Sharshar, 2015).

Hypertension is a well-known risk factor for cognitive impairment and dementia (Deckers et al., 2015). Patients with new-onset dementia had a tendency towards a more pronounced reduction in MAP during anaesthesia. One reason might be that chronic hypertension, with higher sympathetic tone, stiffer blood vessels and altered haemodynamic regulation, makes the cardiovascular system more susceptible to the effects of vasodilatation and sympatholysis caused by anaesthesia (Iadecola and Davisson, 2008). Higher postoperative blood pressure values could also be a result of the correction of intraoperative hypotension, either with vasopressors or blood transfusions. We did not find that high blood pressure values were associated with delirium, indicating that the impact of hypertension on cognitive functioning is more chronic than acute. Our finding can be a result of undiagnosed pre-fracture hypertension.

It could also be that patients with a subclinical neurodegenerative disease (e.g., undiagnosed dementia) have a dysregulation of blood pressure, making them more prone to perioperative hypotension (O'Callaghan and Kenny, 2016). The individual autoregulatory MAP threshold for adequate brain oxygen supply varies among patients, and MAP values well tolerated in some patients may be inadequate in others (Hori et al., 2014, Hori et al., 2016).

We were surprised to find that the association between perioperative use of adrenergic agonists and new-onset dementia was statistically significant, even after adjusting for perioperative decrease in MAP, suggesting that the use of vasopressors might not only indicate relative or absolute hypotension. The same trend was present, although not statistically significant, among patients free from pre-fracture cognitive impairment who developed delirium postoperatively.

A causative role of vasopressor use on new onset dementia is absolutely unclear and maybe unlikely. However, this finding is biologically interesting. Low cerebral tissue oxygen saturation (SctO₂) might

be associated with poor postoperative cognitive outcomes (Slater et al., 2009). Phenylephrine bolus treatment is found to decrease cerebral tissue oxygen saturation (SctO₂), even when MAP increases (Meng et al., 2011). Elderly brains are probably more vulnerable to ischemia, as many have pre-existing neurodegenerative or neurovascular pathology. Thus, they may be more prone to adverse effects of transient falls in SctO₂ than otherwise healthy younger patients. It has been suggested that giving phenylephrine in order to avoid organ ischemia and hypoxia may actually have the opposite result (Meng et al., 2011). Thus, the routine use of vasopressors may be less beneficial than previously thought. The potential mechanisms are unknown. Vasoactive amines do not cross the blood-brain barrier, so neither phenylephrine nor ephedrine is expected to act directly on cerebral arteries (Olesen, 1972). Vasopressors might act indirectly via reflexively increased sympathetic nerve activity leading to constriction of cerebral resistance vessels (Meng et al., 2011). It should be emphasised that these are theoretical speculations and the findings need to be investigated in a prospective and more conclusive study later, as this study was not primarily designed for exploring this relationship.

9.2.3 Autonomic cardiovascular control in patients with delirium

Based on the hypothesis that aberrant stress responses are involved in delirium pathophysiology, involving alterations in the autonomic nervous system (ANS) activity, we wanted to explore possible differences in autonomic cardiovascular control in patients with delirium. The ANS activity can be indirectly assessed by measuring the heart rate variability (HRV). By giving an orthostatic challenge (e.g., head-up tilt testing [HUT]), the ANS must compensate to maintain cardiovascular homeostasis. See also chapter 3.3.7.

Our material is small (14 patients) and only 5 patients were delirious. However, it appears to be some interesting differences between patients with and without delirium:

There was a non-significant trend that both HR and BP values increase more during HUT in the delirious group. A possible explanation for this difference in MAP values is different central set-points of MAP between the groups. If patients in the delirium group have a higher MAP set-point, the HR and TPRI will increase more in delirious patients to reach this set-point during HUT (Stauss, 2002).

The resting values of HRV variables, both in the frequency and in the time domain, indicate that patients with delirium had a stronger autonomic modulation of the sinus node. At rest, patients with delirium tend to have higher HRV indices, in particular indices indicating parasympathetic control (such as HFabs, pNN50 and RMSSD), but also sympathetic modulation might be higher, as LFabs is a result of both sympathetic and parasympathetic activity. This results in higher values of PSD and SDNN (total variability) seen in the group with delirium. During tilt, the variability tends to fall in the delirium group (indicated by a larger reduction in PSD and SDNN) as opposed to the no delirium group.

The patients in the delirium group had a lower functional level (NEADL) before hospitalisation, as well as higher levels of inflammatory markers (CRP and leukocytes) than the control group. Frailty, cognitive impairment and infection are previously shown to be negatively associated with HRV (Parvaneh et al., 2015, Huang et al., 2016, Papaioannou et al., 2009, Zeki Al Hazzouri et al., 2014, Kim et al., 2006, Zulli et al., 2005). We would thus expect lower HRV in the delirium group than in the controls. However, our findings might indicate the opposite.

Autonomic function has hardly been investigated in delirious patients before, and we are aware of only one previous study investigating HRV in patients with delirium (Zaal et al., 2014). Zaal et al. analysed HRV measured in the frequency domain in 25 ICU patients (13 with delirium) and did not find any significant differences between patients with and without delirium. However, the direction of their results were that mean HFnu (indicating parasympathetic activity) were higher in patients with delirium (67 vs 57), particularly in the hypoactive state, and that the LF/HF-ratio (indicating sympathovagal balance) were lower in delirium. The trend was the same as in our study: HFnu at rest 79 (delirium) vs 71 (no delirium) and at tilt 77 vs 61. LF/HF-ratios in our study were: at rest LF/HF 0.3 vs 0.4 and at tilt 0.3 vs 0.5, in patients with and without delirium respectively. In the study by Zaal they used log-transformed data for analysis of LF/HF-ratio, so direct comparisons are difficult.

Usually, the autonomic modulation will increase during head-up tilt. In contrast, the patients with delirium had a fall in many indices, resulting in a lower total variability in the delirium group. Further, we found no increase in the LF/HF-ratio (increased sympathovagal balance) in patients with delirium, as is normally seen during orthostatic stress. These results are difficult to interpret. One possible explanation for the lack of variability increase during tilt in the delirium group might be that they are using their maximal capacity for autonomic modulation already at rest. They have already been brought to the fringe of their buffering capacity, and a further challenge (such as HUT) brings them "outside" the range of their homeostatic control systems, and thus variability does not increase as expected (Staass, 2002, Goldstein, 2001).

Generally, high modulation is a sign of a healthy and robust regulation system that can compensate adequately to external changes in order to maintain normal homeostasis (Goldstein, 2001). The decrease in ANS modulation at tilt might indicate less robust homeostatic mechanisms in patients with delirium.

9.2.4 Clonidine - pharmacokinetics and hemodynamic responses

Previous knowledge about the drug clonidine is presented in chapter 3.5. As a part of the LUCID project, we analysed the plasma concentration of clonidine in 10 geriatric patients with delirium. We were aiming for concentration levels between 0.4 and 0.7 µg/L.

Loading doses

The step-wise regimen with repeated doses of 75 µg every 3rd hour, up to a maximum of 300 µg the first day, was effective and resulted in plasma concentration levels in the higher end of the expected therapeutic range. We aimed for plasma concentration levels between 0.3 and 0.7 µg/L, and calculated theoretically that C_{max} at day one should be lower than 1.2 µg/L (Paper IV). No measurements showed higher values than 1.0 µg/L, but many samples are missing after the last dose at day 1, and we cannot rule out that some patients had concentrations above 1.2 µg/L. Also, the trough concentration at day 2 is in the higher end of our pre-specified target concentration, as it would rise to an even higher C_{max} after the consecutive dose is taken.

After the very first dose of clonidine 75µg, the median plasma concentration levels were in the expected range of approximately 0.3 µg/L. Our findings are in line with previously published studies of plasma concentrations of clonidine in younger adults (Anavekar et al., 1982) where it was shown that a single dose of 75 µg clonidine gave concentration max of 0.285 (+/- 0.001) µg/L. The lower

inter-patient variability in that study compared to this study is likely due to a more homogeneous, younger population and emphasizes the difficulties in pharmacological treatments in the geriatric population.

Steady state

The clonidine concentration levels measured in steady state (day 4-6) are within the target range. After the initial loading doses, clonidine 75 µg twice daily was sufficient to reach trough concentrations (C_{null}) at median 0.47 µg/L, rising to a median level of 0.74 µg/L (C_{max}) after intake of another 75 µg clonidine. These results are also in line with previous studies (Fagermoen et al., 2012, Hogan et al., 1981, Anavekar et al., 1989). See also chapter 3.5.2.

Hemodynamic effects

Clonidine has well known antihypertensive effects and lowers the heart rate, and the maximum hypotensive effect and bradycardia are related to dose and peak plasma concentrations (Anavekar et al., 1982, Anavekar et al., 1989). Therefore, the hemodynamic changes with a trend of lower BP and HR during clonidine treatment were as expected as we reached the assumed therapeutic range. The trend in reduction in SBP, DBP and heart rate in patients treated with clonidine was not statistically significant (except for SBP after the 4th loading dose), but this may be due to the low number of participants. Also, a great variability in blood pressure and heart rate values would be expected in a geriatric hospital population due to natural course of the illnesses and other treatment received. Important is, that even if the median blood pressure and heart rate values were lower in the patients that received clonidine, the values were not below what could be considered safe.

Even if the plasma concentration levels of clonidine occasionally were higher than 0.7 µg/L, this dosage regimen did not have any hemodynamic effects considered unsafe in the observed patients and the protocol seems safe.

9.3 Methodological considerations

9.3.1 General challenges in studies of potential biomarkers in delirium

Two of the papers in this thesis are about potential biomarkers in delirium: paper I about markers of neuroinflammation in serum and CSF, and paper III about autonomic cardiovascular control. There are some important general challenges in studies of potential biomarkers in delirium (Marcantonio et al., 2006):

- 1) Delirium is a clinical condition, the diagnosis is based on a clinical assessment. The diagnostic criteria used or the assessments used for diagnosing delirium often differ between studies (see chapter 3.1.1). Thus, unfortunately there exists no “gold standard” for the diagnosis.
- 2) Delirium is by definition characterized by a fluctuating course. It can be very difficult to establish exactly the time of onset and termination of delirium. In an acute care setting, the patient is usually unknown to the staff. It might be obvious that the patient has some cognitive problems, but hard to separate these from a possible chronic condition. It can be difficult to tell when the delirium has resolved, especially in patients with a pre-existing dementia.

3) Delirium is a CNS process. In general, most biomarkers in delirium research have been studied in blood. The correlation between blood levels and intracerebral levels are most often unknown, making it difficult to draw inferences about brain levels of these biomarkers. Systemic levels of biomarkers may not necessarily reflect pathophysiological processes that are ongoing within the brain. CSF samples are more representative to intracerebral changes than blood, but still these biomarkers are indirect measures of CNS activity. There are very few CSF studies in delirium. Further, even levels in the CSF might not correspond to activity in the brain tissue (the site of lumbar puncture is still far from the brain cells). The use of imaging techniques and electroencephalography (EEG) (van der Kooi et al., 2015) might overcome some of these challenges and more directly reflect the CNS activity.

4) Delirium has many different predisposing and precipitating causes. It can be difficult to isolate markers of delirium from markers of the pre-existing pathology (e.g., undiagnosed dementia or frailty) or changes due to the precipitating cause (e.g., infections, tissue damage and subsequent inflammation).

5) The cross-sectional design is a challenge in biomarker studies. In general, most studies of biomarkers in delirium, both in blood and in CSF, have a cross-sectional design. Accordingly, the patients will be in different delirium categories: Some have no delirium, some have ongoing (=prevalent) delirium, and some patients may not have delirium at the time the sample was taken, but develop delirium later (=incident delirium). Thus, a biomarker can represent a risk factor as well as a marker for an ongoing pathological process.

6) Most patients with delirium (at least outside the ICU) have underlying dementia. For some biomarkers, the level might be elevated in delirium, but decreased in dementia, or vice versa. As most patients with delirium also have underlying dementia, delirium and dementia may level each other out, if chronic cognitive impairment is not taken into account in the analyses. This is one of the main reasons it is important to stratify the analyses according to pre-existing chronic impairment. However, when dividing the study samples into subgroups, there will be few patients in each category, giving limited statistical power, and increasing the risk of type 2 errors.

9.3.2 Blood pressure assessments

In paper II, we examined risk factors for incident delirium and new-onset dementia in a large sample of almost 700 hip-fracture patients. Some methodological issues should be discussed.

The quality and validity of the blood pressure assessments are of great importance in paper II. In our study, MAP was calculated as $[(SBP + (2 \times DBP))/3]$. BP was measured non-invasively and analysed as a continuous variable, but relevant thresholds were also explored: a MAP < 60 mm Hg, a MAP < 50 mm Hg, a MAP decrease > 30% and a MAP decrease > 40% relative to admission MAP. Unfortunately, we did not register the duration of hypotensive episodes or the possible cause. We did not have a clear definition of what is considered hypotension. Different heterogeneous definitions of hypotension have been used in studies of different patient populations and settings (Hirsch et al., 2015). A further limitation is that we only registered BP once preoperatively and postoperatively.

A relevant consideration is whether measurement of arterial BP is the best method to evaluate cerebral hypoperfusion. A recent study monitored 110 patients with near-infrared spectroscopy

(NIRS) to assess the optimal MAP by CBF autoregulation monitoring (Hori et al., 2016). The authors found that BPs above the upper limit of CBF autoregulation were associated with postoperative delirium, and concluded that perioperative BP management might have an effect on the incidence of delirium. They suggest future studies to observe the effect of BP outside the limit of cerebral autoregulation.

As a post-hoc secondary analysis, no statistical power evaluations were conducted to ensure adequate power for the hypothesis explored. The results must be seen in the context that we had a relatively small number of cases of new onset dementia. As a result, our multivariate model, though significant, might have been 'over-fitted', which could impact on the external validity of our findings.

9.3.3 Head-up tilt testing

The HUT- study was designed to assess possible differences in hemodynamic and autonomic responses in elderly patients with and without delirium. The study had a cross-sectional design and was carried out in geriatric in-patients with an infection. Due to multimorbidity, some patients were not eligible, especially because of atrial fibrillation and the use of beta-blockers. These exclusion criteria are very common among indwelling geriatric patients, and the recruitment of patients to the study was time-demanding. The study had an explorative approach and was carried out as a pilot study. We were not aware of any other studies assessing autonomic functions in delirious patients, and we were not absolutely sure if the HUT test was feasible in patients with delirium. The number of participants was low, and the study is too small to draw conclusions. This may impair the generalizability of our findings.

We studied the autonomic responses during HUT using non-invasive methods, but autonomic function can be assessed also by other methods, e.g., either by intraneural microneurography or by measurements of catecholamines, their precursors and metabolites (Freeman, 2006). The non-invasive approach was chosen because we had previous experiences in our research group with the methods (Mellingsaeter et al., 2015), and because it was considered less harmful for the patients. This is a substantial advantage because invasive procedures affect the autonomic nervous system just by applying them. Indirect methods are however associated with more uncertainty, as the measurements must be interpreted to give understandable information about the system we want to investigate.

A pre-defined, standardized protocol including the HUT test was used. We used HUT with a low angle (15 degrees), because of practical reasons. It was possible to tilt the hospital beds to a maximum angle of 15 degrees, and it was considered a benefit that the patients could stay in their own beds during the test. A low-grade tilt to 30 degrees (Smith and Porth, 1991) and 20 degrees (Wyller et al., 2007) are more commonly used in experimental settings, challenging the cardiovascular system, but with less discomfort than HUT with higher angles. Our results (table 2 in Paper III) indicate that the modified HUT to 15 degrees gave physiologically plausible results, even though the orthostatic challenge was small.

Respiration, bladder filling, hydration and fluid balance might influence HRV measurements (Quintana and Heathers, 2014), and was not controlled for in our study. The HUT was conducted under equal conditions for all participants, performed by the same investigator (BEN). It was not feasible in this experiment to control for all potential environment factors, but we did control for

most of them, such as time of day, dimmed lights, warm and quiet room with no talking, meals. Variations in hydration and fluid balance are possible, as the participants were treated for infections.

9.3.4 Delirium assessments and screening

Diagnosis

It can be difficult to diagnose delirium. Some of the diagnostic challenges are already presented in chapter 3.1.1, but here follows some more comments.

Delirium is also called “acute confusional state”, and this particular expression is very commonly used by health care personnel (at least in Norwegian hospitals). However, not all patients with “confusion” are delirious (Richardson et al., 2016). Other conditions, e.g., behavioural and psychological symptoms of dementia (BPSD) present with similar symptoms as delirium, such as irritability or apathy, agitation and delusions (Selbaek et al., 2013). This overlap in symptoms between a chronic neurocognitive disorder and delirium represents a challenge for both clinicians and researchers, and there is a lack of consensus concerning assessment and diagnosis of delirium in these situations (Richardson et al., 2016).

The diagnosis of delirium in patients with known (or sometimes undiagnosed) dementia is commonly referred to as “delirium superimposed on dementia” (DSD) (Fick et al., 2002, Morandi et al., 2017). Most delirium experts use the CAM or apply the DSM-5 criteria directly to assess for the presence of DSD (Richardson et al., 2016). However, neither of these approaches provides specific tests for assessment of attention or arousal, or guidance whether specific tools should be used in patients with dementia or in dementia subtypes (Morandi et al., 2017).

It is essential according to the diagnostic criteria of DSM-5 and ICD-10 to ascertain if the mental disturbance represents a *change* from baseline. This information can be hard to obtain. Sometimes the relatives can describe very well that there has been a rapid change in the patients’ mental condition, but at other times this important information is lacking. Then it might be difficult to assess whether the results of specific attention tests (e.g., months of the year backwards) or the cognitive symptoms (e.g., impaired short term memory, delusions) are representative for the patients normal condition or influenced by delirium. A similar challenge is to assess whether the delirium has resolved and to follow the delirium trajectory (Adamis et al., 2015a). Repeated delirium assessments and cognitive tests are time consuming, and the patients can get tired, annoyed, or feel embarrassed. When has the patient reached its cognitive baseline? Sometimes a *retrospective* diagnosis of delirium at its recovery is the only possibility.

The term “*subsyndromal delirium*” is not well defined (see chapter 3.1.1), and it is not established consensus whether a patient with subsyndromal delirium should be considered a case or a control (see chapter 9.3.1). We decided to include also patients with subsyndromal delirium in LUCID, and sharpened the definition of subsyndromal delirium (compared to the “attenuated delirium syndrome” described in the DSM5 criteria). We could only include patients with a confirmed acute change in attention/consciousness and/or cognition that was not explained by another underlying condition. We defined in our diagnostic algorithm how we diagnosed subsyndromal delirium, see chapter 7.1.4.

These challenges highlight the importance of a transparency of the diagnostic process and to register the different “components” included in the diagnostic algorithm, making it easier to compare studies even if diagnostic criteria might change in the future. In the protocol for LUCID (paper IV), we described in detail what tests we would use to assess arousal, attention and cognition, in order to make the diagnostic process as transparent as possible.

We did not want to include patients where we were not sure this was a condition at the delirium axis. All patients were evaluated by one of the two study physicians (KRH or BEN), and when in doubt we consulted each other or an even more experienced geriatrician (Torgeir Bruun Wyller). We made the decision on an overall clinical assessment, leaning heavily on the tests and diagnostic algorithm described.

Screening

The screening procedure described in chapter 7.1.3 and 7.1.4 was designed to provide a pragmatic set of methods to identify patients with delirium, rather than to be a formal package of measures. The components chosen were designed to provide multiple opportunities for picking up delirium without having to do a full diagnostic assessment on all patients. We were looking for patients who were likely to have delirium rather than needing to get all those who might have delirium – so the combination of measures we used aimed at that.

“Days of the week backwards” might be a specific rather than a sensitive test to delirium. “Months of the year backwards” is more sensitive to delirium but also more sensitive to dementia (Bellelli et al., 2014, Morandi et al., 2017). We thus believe that days of the week backwards was a good choice to detect obvious delirium. Regarding the SQiD – this is really just a form of the ‘acute change’ criterion that is present in all diagnostic criteria for delirium. The SQiD was used as a guide to help address this criterion.

The most important part of the screening process in LUCID was probably that the study physicians were present at the ward on almost every weekday evaluating all new patients in regard to the selection criteria, see chapter 7.1.3. This evaluation was done partly in dialogue with the treating personnel. We ruled out all patients with known obvious exclusion criteria, not to bother them with the study-related screening procedures. We actively asked the personnel for any delirium symptoms. All possible candidates were thoroughly evaluated by the study physicians according to the DSM-5 criteria, as described in chapter 7.1.4.

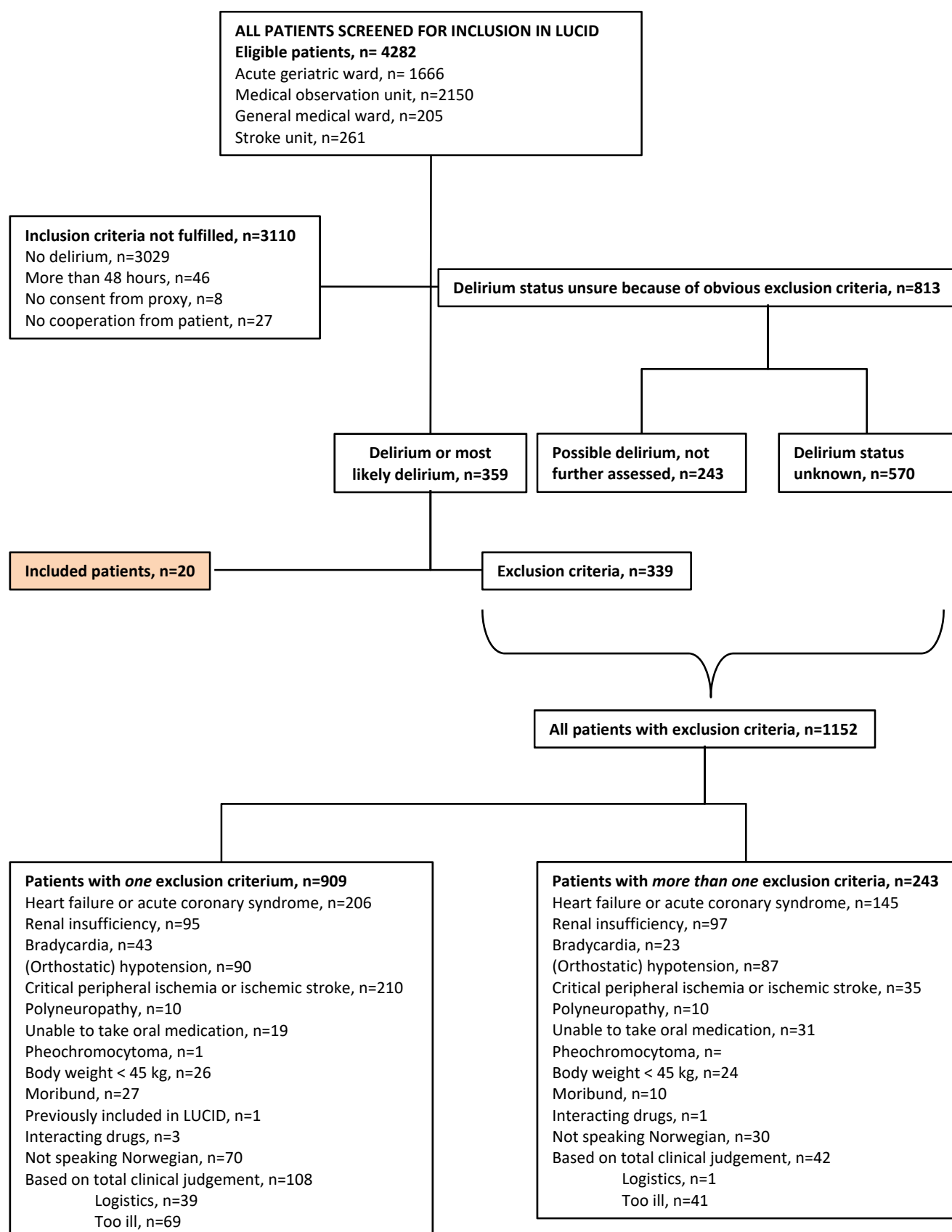
9.3.5 Inclusion of patients in LUCID

A flow diagram for all patients screened for inclusion in LUCID is presented in Figure 8. The recruitment flow charts from each recruitment centre are presented in the Appendix, Figures 10-13.

A total of 4282 patients were assessed for inclusion between April 2014 and February 2017. 20 patients were included (paper V). Most patients were screened at the acute geriatric ward (n=1666) and in the medical observation unit (n=2150). 3110 patients did not fulfil the inclusion criteria, and in addition 1152 patients were not included because of exclusion criteria. 243 of these had more than one exclusion criterion present. The most common reasons for exclusion were heart failure, New York Heart Association functional classification of heart disease (NYHA) class 3 or 4, or acute coronary

syndrome, hypotension and renal insufficiency. In one patient the randomisation code had to be broken due to safety reasons after a possible severe adverse event.

Figure 8. Flow diagram for all patients screened for inclusion in LUCID



Recruitment of patients over a period of almost 3 years resulted in only 20 included patients. The screening was done on a daily basis, except during weekends and summer holidays. Because of a low inclusion rate, we even expanded the screening after some months, to involve patients admitted to other medical wards. Why was it so hard to include patients, and what were the reasons for this low inclusion rate (4282 patients screened, 20 patients included)?

The patients were frail, and had a high number of exclusion criteria present at admission

Most drug trials in delirium have been carried out in patients admitted to surgery (both acute and planned) or in an intensive care setting, and only a few in a geriatric ward/medical ward (see chapter 3.4, and table 20 and 21 in the appendix). Patients admitted to a geriatric ward with acute medical conditions are usually frailer and more vulnerable to adverse events than patients admitted to elective surgery. The 20 patients we included in LUCID (paper V) were old (median 86 years (range 66-95)), with multimorbidity, and most often with a pre-existing functional and cognitive impairment.

The incidence of delirium in the recruitment period

In a such frail population, a high prevalence of delirium would be expected. Based on our screening results from the acute geriatric ward (figure 10 in the Appendix), 204 of 1666 patients had delirium, and 113 of 1666 had possible delirium. Thus, close to 1 of 5 patients (317/1666 patients = 19%) admitted to the ward had delirium/possible delirium. This delirium incidence was as expected, and is within the range of what is previously described (Ryan et al., 2013, Pendlebury et al., 2015).

Were the exclusion criteria too strict?

The main reason the inclusion rate was so low, was the exclusion criteria. The most common reported exclusion criteria were heart failure (acute exacerbation or NYHA class 3-4), acute coronary syndrome, too low blood pressure (or known orthostatic hypotension) and kidney failure. However, several patients (n=243) fulfilled more than one exclusion criteria.

We considered several times during the inclusion period whether it would be possible to remove one or some criteria. However, we did not find this safe. Even when we followed the criteria, we had 3 deaths among the 20 included participants; 1 in the clonidine group and 2 in the placebo group (paper V). This illustrates the frailty of this population. One of the exclusion criteria was “any other condition as evaluated by the treating physician”. We sometimes concluded, based on a comprehensive assessment, that the patient was not suitable for participating in a drug trial with clonidine. Some of these patients actually did fulfil the selection criteria, but were multimorbid, very frail and clinically unstable. In almost all these cases, it emerged that this was the right decision, as these patients got worse or died.

We did not include patients during weekends, and 46 patients were maybe missed because we assessed them more than 48 hours after admission. However, based on the overall inclusion rate, it is unlikely that more than a very few of these patients would really have been included anyway.

Consequences of the low inclusion rate

Even if LUCID had turned out to give results in favour of treatment of delirium with clonidine versus placebo, the external validity of the findings needs to be discussed. In real life, hospitalised patients with delirium are often the most vulnerable (high predisposition) and/or the most severely ill (strong noxious insult) (Inouye, 1999). We have *not* studied the effect of clonidine on delirium (or on hemodynamic variables) in patients with NYHA 3 to 4 heart failure, hypotension, or eGFR below 30

ml/min. Thus, our sample of the included 20 patients does not mirror the whole population at highest risk of getting delirium.

We have included 20 participants in LUCID after screening 4282 patients. As a consequence of this, we have decided to end the study prematurely. Some arguments for this decision are: it is time-consuming and resource-demanding (researchers), the findings is losing external validity (even if we expanded the study to other sites, the rate of included patients would still be low, or even lower). There is a balance between these two points; it would indeed be a good thing to invest that many resources and time provided that the external validity of the findings had been higher.

We have not analysed the effect of clonidine on delirium yet (the primary endpoint in LUCID). Even if our results presented in paper V indicate that clonidine treatment can be safe, the population included in the study is selected, compared to a real life acute geriatric population.

9.3.6 Clonidine - from planning to plasma concentration values

There is a long way from initiating a pharmacological study to actually obtaining the results of plasma concentration values. The LUCID project has been hard, work-demanding and time-consuming. It has also involved many persons - and several things could easily have gone wrong. We theoretically calculated the dose of clonidine considered appropriate to reach a specific plasma concentration level, and we designed the dosage plan. The study medication was prepared and labelled according to a randomisation code. The medication was transported to the hospital, and stored at the ward for a long time. The administration of the drug was done by the nurses at the ward, from the right box to the correct patient exactly as scheduled. The blood samples were taken at the right time by the study physicians or the research assistants. The blood was centrifuged and stored appropriately. The correctly identified aliquots with frozen plasma were transported to the laboratory at another hospital for proper analyses. Finally, the investigators (KRH and BEN) received an email with the laboratory results. The point is - all elements included in this process had to be planned and carried out really carefully to obtain the final results. In most drug trials, all of this is done by a pharmaceutical company with many employees and large financial resources. Non-profit studies are rare in drug treatment, and even less often the researchers do so much themselves.

Missing data

Despite the effort to obtain all blood samples and blood pressure measurements, there are some missing data (paper V). The overall reason was the consideration for the patient's best. Some patients did not cooperate well enough, so it was not possible to obtain the planned blood samples voluntarily. This is a well known challenge in carrying out research in patients with cognitive and behavioural problems. In some of the patients there were technical difficulties during the blood sample procedure (invisible and small veins, large hematomas, etc.). It was considered unethically and clinically inappropriate to wake up patients asleep at midnight to obtain blood samples.

9.4 Strengths and weaknesses of this work

Several methodological issues have already been discussed, and are also thoroughly presented in each paper I-V. A summary of the major limitations and strengths is presented here.

Limitations:

- Small sample size (paper III and V) and small subgroups (paper I and II) limit the statistical power for analyses and leave the confidence intervals wide.
- Some delirium assessments were missing (preoperative delirium data and no formal delirium assessments on weekends in paper I and II).
- Possible biomarkers (paper I and III) were analysed only at one point in time.
- A cross-sectional study design (paper I and III) make it impossible to draw conclusions regarding causality.
- Liquid from a lumbar puncture is not the same as brain tissue. Autopsies or brain imaging techniques could reflect the pathological processes even more directly than CSF (paper I).
- The measurements of perioperative hemodynamic variables were not standardised between the two studies, and the duration of hypotensive episodes was not registered (paper II).
- Time to follow-up was different in the two cohorts (paper II).
- We did not control for respiration or fluid balance during registration of HRV measurements (paper III).
- Due to multimorbidity, several patients were not eligible (paper III-V). This may impair the generalizability of our findings.
- Some plasma concentration samples were missing (paper V).

Strengths:

- The merging of cohorts (paper I and II), made pooled analysis possible. The sampling procedures across centres were similar.
- Persons with pre-existing dementia could be included in all studies. Nursing home residents were not excluded (except in Edinburgh, sample 3).
- Follow-up allowed us to study long term cognitive outcomes (paper II and IV).
- We used CSF to analyse possible biomarkers. Biomarkers in CSF are more representative for neuropathological changes than biomarkers in blood (paper I).
- CRP, IL-6 and IL-6R were measured by ELISA (paper I).
- Validated tools were used for assessment of delirium and pre-fracture cognitive decline. A formal delirium diagnosis by DSM or ICD criteria, or a method based upon this (e.g., CAM) was made.
- HRV was explored in both the frequency domain and time domain, using a well-defined, standardized protocol including a tilt test.
- The patients were included in a well designed RCT with a published protocol, and the patients were monitored very closely (paper IV and V).
- There was a clear pre-defined expectation on plasma concentration levels (paper V).
- Hemodynamic changes caused by clonidine were assessed by comparing a real life, matched, control group (paper V).

10 Conclusions and suggestions for future research

Neuroinflammation

The neuroinflammatory hypothesis of delirium is a leading hypothesis. Based on animal studies (Cunningham et al., 2005) and the general knowledge about inflammation (Cerejeira et al., 2010), pro-inflammatory cytokines such as IL-1, IL-6 and TNF alpha should be elevated, whereas anti-inflammatory markers as IL-10 should be reduced in patients with delirium. The current findings in studies of CSF inflammatory biomarkers in delirium are inconclusive, but do not necessarily refute the neuroinflammatory hypothesis. Some studies are lending some support to the neuroinflammatory hypothesis, and other studies - like paper I in this thesis - present a challenge to the model as currently presented. Underlying dementia neuropathology, small studies, mixed delirium aetiology and timing of CSF sampling might be reasons for the potential conflicting findings.

Delirium and dementia

A recent publication clearly shows the synergistic effect of dementia and delirium, and that cognitive decline after delirium is not just an acceleration of the underlying pathologic process of dementia (Davis et al., 2017). The understanding of the pathophysiology of delirium and its relationship to dementia remains unclear and future research is needed to enhance our understanding of the delirium pathology and its relationship to dementia (Fong et al., 2017).

Autonomic nervous activity

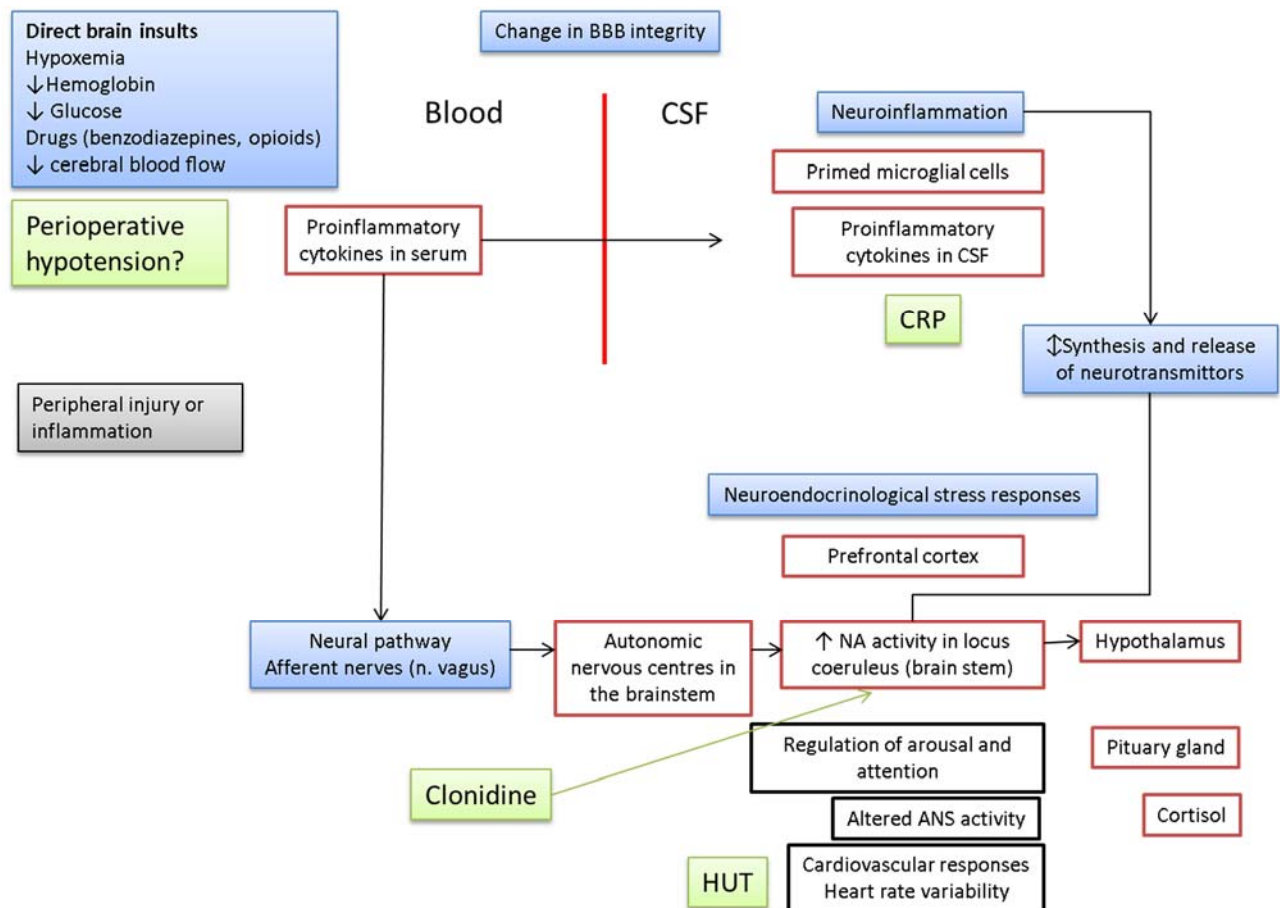
The findings in the HUT study in paper III suggest possible differences in autonomic cardiovascular control in patients with delirium. An explanation for our findings *could be* alterations in central autonomic networks and in the prefrontal cortex, as discussed in chapter 9.2.3. Central structures in the brain stem, such as locus coeruleus (synthesising noradrenaline), are important parts in regulation of arousal and attention and project to most other brain areas, including the hypothalamus and HPA-axis (Brodal, 2013, Goldstein, 2001). More studies are needed to assess the possible role for these central structures and networks in delirium pathophysiology.

Clonidine - still an option in delirium treatment?

Based on pilot work presented in this thesis, there seems still to be a theoretically good rationale to expect a beneficial effect of clonidine in patients with delirium. We have presented a feasible dosage regimen and provided a good starting point for future studies. To reach a large enough sample size, and due to strict exclusion criteria and safety issues, clonidine would probably be better explored in a less frail population.

Figure 9. Some proposed pathways linking peripheral insults to CNS changes hypothesized to lead to delirium.

Elements in blue represent suggested pathophysiological pathways; elements in green are hypotheses explored in this thesis; elements in red represent some possible CNS structures and mediators involved in delirium; the black boxes name some clinical features particularly relevant in this thesis.



Suggestions for future research

Evidence suggests a role of inflammation in delirium, but also biomarkers related to other possible pathological processes should be examined. Neuroimaging markers, Alzheimer disease biomarkers, genomics, proteomics and metabolomics, as well as markers of neural injury, blood-brain barrier disruption and endothelial damage could be explored. It is important to study these markers in the light of dementia pathology and to look for shared mechanisms between delirium and dementia pathology.

It is still interesting to explore the autonomic nervous activity in patients with delirium, as previous results and the study presented here are inconclusive and suggest a possible altered activity in delirious patients. However, the HUT method used in this work might be too complicated and give

too small patient samples. Other possibilities could be to obtain samples of neurotransmitters in CSF, blood or in urine, or to assess HRV by more easily available methods (e.g., only during supine rest)

In future research, it would be valuable to have longitudinal data and repeated CSF samples (or other samples) to follow trajectories of the biomarkers, although this would however be practically and ethically challenging. Larger multisite studies would make it feasible to study potentially different pathophysiological mechanisms in different subgroups. International collaboration between research groups might conduce to larger samples and a more standardised methodology in future delirium research.

Final remarks

This thesis presents five papers with very different approaches, but they all have in common that they shed light on unanswered questions in delirium research: pathophysiology, risk factors, cognitive trajectories, diagnostics and pharmacological treatment. This work has hopefully contributed to the growing field of delirium research; we have used new methods of exploring delirium pathophysiology; we have launched a drug not previously well studied in delirium treatment, and explored whether this treatment is feasible and safe; we have made a transparent description of the diagnostic process. Our research group has learned a lot through these studies, and is excited to continue exploring unresolved problems within the research field of delirium.

“NOW THIS IS NOT THE END. IT IS NOT EVEN THE BEGINNING OF THE END. BUT IT IS, PERHAPS, THE END
OF THE BEGINNING.”

Winston Churchill, 1942

11 References

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12 Appendix

Table 20. Pharmacological trials for *prevention* of delirium. n = sample size

Author	The drugs that are studied	n	Study design and population	Results	Basis for delirium diagnosis
Antipsychotics					
Kalisvaart et al., 2005	Haloperidol (n=212) orally 0.5 mg x 3/day starting on hospital admission, continued until 3 days after surgery vs. Placebo (n=218) If post op delirium: haloperidol and/or lorazepam 3 times a day	430	RCT, double-blind Hip-surgery, acute or elective, >70years, delirium free at admission Mean age 79 +/-6y Study group in generally good condition (low APACHE2, high Barthel)	No difference in delirium incidence: haloperidol 15% vs placebo 17%, RR 0.91 [95% CI 0.59-1.42], but decreased duration, severity, and LOS Duration: 5.4 vs 11.8 d (p<.001) Severity: DRSR98 14 vs 18 (p<.001) Hospital stay: 17 vs 22d (p<.001)	CAM and DSM-IV DRS-R-98, MMSE, Digit span
van den Boogaard et al., 2013	Haloperidol (n=177) iv 1 mg/8h until discharge vs no haloperidol (historical control group, n=299)	476	Historical controlled trial Medical and surgical ICU patients at high delirium risk Mean age 63	Reduced incidence of delirium (65% vs 75%, p=0.01) and more delirium-free days in haloperidol group	CAM-ICU, RASS
Hakim et al., 2012	Early treatment with risperidone (n=51) orally 0.5 mg/12 h vs placebo (n=50) for subsyndromal delirium	101	RCT After on-pump cardiac surgery in the elderly, 65 years or older	Lower delirium rate in risperidone group (14%) vs placebo (34%), p= 0.03. No difference LOS in ICU or hospital.	DSM-IV, ISDSC
Wang et al., 2012	Haloperidol (n=229) 0.5mg bolus iv, cont. infusion 0.1mg/h for 12 hours vs. placebo (n=228)	457	RCT, double-blind Patients 65 years or older admitted to ICU after non-cardiac surgery Mean age 74 +/-6y	Lower incidence of delirium within first 7 postop days: 15% vs 23% (p=0.03). No difference in length of stay, postop complications or mortality. No drug related side-effects	CAM-ICU, RASS
Vochteloo et al., 2011	Haloperidol (n=173) orally 1 mg/12 h day 1, vs no haloperidol	378	Hip fracture surgery, not randomised, haloperidol given to high-risk patients. Compared to historical data	Prophylactic treatment of high-risk group did not reduce delirium incidence	DSM-IV
Prakanrattana and Prapaitrakool, 2007	Risperidone (n=63) 1 mg or placebo (n=63) sublingually as a single dose when they regained consciousness	126	RCT, double-blind Drug administered soon after recovery from anaesthesia after elective cardiac surgery Mean age 61 +/-10y	Lower incidence of postop delirium, 11% vs 32%, p=0.009. No difference in LOS, ICU days or postop complications.	CAM-ICU
Fukata et al., 2014	Haloperidol (n= 59) 2.5 mg iv at 6.pm from po days 1 to 3 vs control (n=60)	119	Randomised open-label prospective study. Elective abdominal or orthopaedic surgery, age >75 y.	No reduced incidence of delirium: 42% in intervention group vs 33% in control group	NEECHAM

Larsen et al., 2010	Olanzapine (n=196) 5 mg orally x 2 vs placebo (n=204) just before and after surgery	495	RCT, double blind Elective knee-/hip-replacement Mean age 74 +/-6y	Reduced incidence of delirium 14% vs 40%, NNT=4 Greater duration and severity in olanzapine group Drop-out n=95, no ITT analysis	DSM-III-R, DRS-R-98, CAM
Cholinesterase inhibitors					
Youn et al., 2016	Rivastigmine (n=31) patch 4.6 mg vs. no patch (n=31). From 2-3 days before operation to 7 days postoperative.		Randomised, single-blind Hip-fracture surgery Patients with cognitive impairment	Lower incidence of postoperative delirium in rivastigmine group (5/31) vs the other group (14/31), p=0.01, with lower severity	CAM, MMSE, DRS
Gamberini et al., 2009	Rivastigmine (n=56) 1.5 mg x 3 vs placebo (n=57) Rescue medication: haloperidol (start 0.5 mg/6 to 8h) and lorazepam (1 mg per day)	120	RCT, double-blind. Elective cardiac surgery, Mean age 74y Medication from the day before surgery until 6 th po-day	No significant difference neither in delirium incidence (32% in rivastigmine group vs 30%, p=0.8) nor the use of rescue medication	CAM (used both in the surgical and ICU setting)
Liptzin et al., 2005	Donepezil (n=39) 5-10 mg/day vs placebo (n=41)	80	RTC, double-blind. Elective joint-replacement. Mean age 67 +/-9y Medication from 14 days before to 14 days after surgery.	19% delirious, no significant difference between groups in occurrence or duration of delirium or subsyndromal delirium. Inadequate levels of missing data (over 20%)	DSM-IV, CAM
Zaslavsky et al., 2012	Rivastigmine transdermal (n=11) vs placebo (n=17)	28	RCT, double-blinded in patients at risk for postoperative delirium (elective surgery). Age > 65 years	No difference in delirium incidence, but higher postoperative MMSE values in the treatment group. The study was halted early because of the results of van Eijk (warning from manufacturer)	CAM
Sampson et al., 2007	Donepezil (n=19) 5 mg vs placebo (n=14)	33	RTC, double-blinded After elective hip-replacement. Mean age 67y. Medication immediately after surgery and every 24 th hour for 3 days	No significant difference in delirium incidence (21%) or LOS. There was a trend suggesting positive benefit.	Delirium Symptom Interview
Alpha-2 adrenoceptor agonists					
Shehabi et al., 2009	Dexmedetomidine (n=154) 0.1-0.7 µg/kg/h vs morphine (n=152) 10-70 µg/kg/h	306	RCT, double-blinded, 2 centres After cardiac surgery Mean age =71y	No significant difference in delirium incidence (9% vs 15%, RR 0.57, 95% CI 0.26-1.1, p=0.09), but reduced duration (2 vs 5 days, p=0.03)	CAM-ICU
Pandharipande et al., 2007	Dexmedetomidine (n=54) 0.15 µg/kg/h vs lorazepam (n=52) 1 mg/h Max: 1.5 µg/kg/h dexmedetomidine or 10 mg/h lorazepam	106	RCT, double-blind, 2 centres Mechanically ventilated medical and surgical ICU patients	No significant difference in delirium incidence (79% vs 82%), duration or mortality, but more days alive without delirium or coma in the	CAM-ICU, RASS

			Mean age 60 years	dexmedetomidine group (7 vs 3, p=0.01)	
Riker et al., 2009	Dexmedetomidine (n=244) 0.2-1.4 µg/kg/h vs midazolam (n=122) 0.02-0.1 mg/kg/h	375	RCT, double-blind 68 centres, 5 countries Medical and surgical mechanically ventilated. Mean age 62 +/-15y	Lower prevalence of delirium in dexmedetomidine group (54% vs 77%, p=0.001).	CAM-ICU, RASS
Maldonado et al., 2009	Dexmedetomidine (n=40) 0.4 µg/kg bolus, then 0.2-0.7 µg/kg/h vs midazolam (n=40) 0.5-2 mg/h vs propofol (n=38) 25-50 µg/kg/min	118	Randomized, open-label Postoperative after elective cardiac surgery, mean age approx. 55-60y	Lower incidence of delirium in dexmedetomidine group (3%) vs 50% in both midazolam and propofol group. NNT=2.1	DSM-IV-R
Djaiani et al., 2016	Dexmedetomidine (n=91) 0.4 µg/kg bolus, then 0.2-0.7 µg/kg/h vs propofol (n=92) 25-50 µg/kg/min	185	RCT, single-blinded Cardiac surgery, 60 years or older Mean age 73years	Lower incidence of delirium in dexmedetomidine group (18% vs 32 %, OR 0.46, p=0.028) Also shorter duration of delirium (2 vs 3 days, p=0.04) and lower use of antipsychotics in dexmedetomidine group	CAM-ICU + CAM (ward)
Su et al., 2016	Dexmedetomidine (n=359) 0.1 µg/kg/h the first postop night vs placebo (n=350)	700	2 sites RCT, postop ICU after non-cardiac surgery, both mechanically ventilated and not. Age 65 and older	Reduced incidence of delirium first 7days (OR 0.35, 95% CI 0.22-0.54). Shorter ICU LOS. Safe.	CAM-ICU, RASS
Liu et al., 2015	Dexmedetomidine (n=100) 0.2-0.4µg/kg/h during surgery (general anaesthesia) vs placebo (n=100)	200	Elective hip/knee/shoulder replacement. Double-blinded	Significantly lower incidence of delirium in dexmedetomidine group, but difficult to interpret the data in the paper.	CAM
Melatonin-receptor agonists					
Sultan, 2010	Melatonin (n=53) 5 mg vs. control (n= 49) vs midazolam (n=50) 7.5 mg vs clonidine (n=51) 100 µg	203	Controlled, no placebo, double-blinded Elective hip surgery with spinal anaesthesia. Mean age 71 +/-7y	Lower rates of delirium in melatonin group vs the other groups. No effect on LOS. Delirium incidence: 10% melatonin vs 33% control, p=0.003	Abbreviated mental test (AMT)
de Jonghe et al., 2014	Melatonin (n=219) 3mg vs placebo (n=225) At 21:00 for 5 days	452	RCT, double-blind, 3 centres Acute hip-fracture Mean age 84 years	No significant difference in incidence of delirium (30% in melatonin group vs 26%) or duration. A smaller proportion in melatonin group had a long-lasting delirium >2 days, p=0.02.	DSM-IV, DOS
Hatta et al., 2014	Ramelteon (n=33) 8 mg vs placebo (n=34) Every night for 7 days	67	RCT, rater-blinded, 5 centres Medical patients 65-89 y 43 patients in acute medical wards, and 24 in ICU	Lower incidence of delirium in ramelteon group (3% vs 32%, p=0.003). Observation period 1 week.	DRS-R-98 DSM-IV

Al-Aama et al., 2011	Melatonin (n=72) 0.5 mg vs placebo (n=73) Daily at night for max 14 days	145	RCT, double-blind Admissions to medical unit, Mean age 84 +/-6y	Lower incidence of delirium in melatonin group (4% vs 19%, p<0.02) (after excluded CAM-pos at enrolment). No significant difference in delirium severity or LOS	CAM, MDAS
Artemiou et al., 2015	Melatonin (n=250) vs control (n=250) 5 mg evening before op and 3 days postop.	500	Prospective observational. No placebo. Elective cardiac surgery.	Incidence of delirium 8% in melatonin group vs 21% in control group, p=0.001	CAM-ICU
Robinson et al., 2014	Tryptophan (n=152) 1 g x 3/d vs placebo (n=149). Started after surgery, cont. up to 3d postop	301	Placebo RCT, double-blinded. Major elective surgery/po ICU. Age>60y	Incidence of hyperactive or mixed delirium: 17% in tryptophan group, 9% in placebo, p=0.18. Overall delirium equal between groups, almost 40%	CAM-ICU, RASS
Other drugs					
Whitlock et al., 2015, Royse et al., 2017	Methylprednisolone 250 mg (n=3755) vs placebo (n=3752) at anaesthetic induction	7507	Multicentre. Undergoing cardiopulmonary bypass procedures	8% delirium in both groups RR 1.02, (95% CI 0.87 to 1.19)	CAM-ICU (Delirium as safety outcome)
Aizawa et al., 2002	Intervention (20 patients): Diazepam i.m. (0.1 mg/kg) and pethidine 1 mg/kg i.m. at 8p.m + flunitrazepam infusion 0.04 mg/kg for 8 hours. Given 3 consecutive nights Control group 20 patients	40	Non-blinded controlled. Open laparotomy abdominal cancer >70 y	Incidence of postop delirium lower in treatment group (5%) than in control group (35%), p=0.02	DSM-IV
Leung et al., 2006	Gabapentin 900 mg po (n=9) preop and 3 postop days vs placebo (n=12)	21	Double-blinded RCT, pilot. Surgery involving the spine, in general anaesth.	5/12 patients had postop delirium in placebo group, vs 0/9 in gabapentin group, p=0.045	CAM, RASS
Pesonen et al., 2011	150 mg pregabalin (n=35) before op, then 75 mgx2 for 5 d or placebo (n=35).	70	RCT placebo controlled Cardiac surgery with CPB >75 years	Lower CAM-ICU score at day 1 (not day2-5) in treatment group. No diff in use of haloperidol	CAM-ICU, RASS, MMSE
Papadopoulos et al., 2014	8 mg ondansetron vs placebo iv daily postop for 5 days	106	Hip-fracture surgery	Lower incidence and duration of delirium on ondansetron group	CAM
Sauer et al., 2014	Dexamethasone (n=367) 1mg/kg or placebo (n=370) at induction of anaesthesia	737	Placebo RCT. Cardiac surgery with CBP	No diff in incidence of delirium (14% in both groups) or duration of delirium.	CAM-ICU

Table 21. Pharmacological trials for <i>treatment</i> of delirium. n = sample size					
Author	The drugs that are studied	n	Study design and population	Results	Basis for delirium diagnosis
Antipsychotics					
Breitbart et al., 1996	Haloperidol (n=11), 2.8 mg 1 st day, 1.4mg/d maintenance vs. Chlorpromazine (n=13) vs. Lorazepam (n=6)	30	RCT, double blinded AIDS –patients Mean age 39 years	Haloperidol and chlorpromazine: significant improvement in delirium symptoms the first 2 days, not thereafter, compared to the lorazepam group. More adverse effects in the lorazepam group	DSM-III-R, DRS
Han and Kim, 2004	Haloperidol (n=12) 0.75mg x 2 vs. Risperidone (n=12) 0.5 mg x 2	28	RCT, double blinded Mixed medical and surgical (4 med wards, 2 ICU, 2 oncol wards), age 65 years	No significant differences in MDAS scores between groups, both groups got better	DRS, MDAS
Skrobik et al., 2004	Haloperidol (n=45) orally 2.5-5 mg (patients over 60 y: 0.5-1 mg) every 8 h, then titrated for up to 5 days vs. Olanzapine (n=28) orally 5 mg/day (over 60 y 2.5 mg/d) Treated within 2 hrs of delirium diagnosis	73	Prospective, randomized trial Medical and surgical ICU, mean age approx. 65 years 48 elective operations, 21 urgent operations, 4 medical patients	Delirium symptoms (DI) decreased in both groups. Olanzapine: no side-effects. Haldol: 6 patients extrapyramidal effects	ICU-DSC, DI, DSM-IV
Tahir et al., 2010	Quetiapine (n=21) 25mg up to max 175mg/d vs Placebo (n=21)	42	Double blinded RCT. 19 postoperative patients (11 hip fractures), 23 medical patients. Mean age 84y	Quetiapine group recovered faster from delirium. Underpowered for treatment comparisons.	DSM-IV, DRS-R-98
Lee et al., 2005	Amisulpride 50-800 mg/day vs. Quetiapine 50-300 mg/day Doses (both are atypical antipsychotics) were flexible according to clinicians preferences	40	Medical ITU and oncology, patients referred to a psychiatric consultation service	DRS-R-98 scores significantly reduced in both groups. No group difference. Sleep quality equal in both groups	DSM-IV and DRS-R-98
Hu et al., 2004	Olanzapine 1.25-2.5 mg initial dose, adjusted to 1.25-20 mg/day vs. Haloperidol intramuscular injection, 2.5-10 mg/day, depending on response vs. Control	175	“Senile delirium” due to metabolic(n=68), toxic (n=47), structural (n=25) or infectious (n=35) causes Type of ward was not stated. The effect was observed for one week; delirium lasting from 30 minutes to 17 days Patients were not blinded; indirect method of assessing delirium	Statistically significant shorter duration of delirium in the haloperidol group.	DSM-IV
Devlin et al., 2010	Quetiapine (n=18) orally 50-200 mg/12h vs. Placebo (n=18)	36	RCT, double-blinded Medical and surgical ICU Mean age approx. 63 years	Quetiapine associated with faster resolution and duration of delirium, and less agitation	ICDSC

Girard et al., 2010b	Haloperidol (n=35) 15mg/day vs. Ziprasidone (n=32) 113 mg/day vs. placebo (n=36)	103	6 centres. RCT, double blinded. Pilot/feasibility study Mechanically ventilated ICU (medical and surgical) patients, mean age 54 years	No difference in number of days alive without delirium or coma (14, 15, 12 days, p=0.66). No difference in mortality No evidence that neither haloperidol nor ziprasidone effectively treated delirium	CAM-ICU
Yoon et al., 2013	Haloperidol (n=23) 0.5-10 mg/day vs Risperidone (n=21) 0.25-4 mg/day Control 1: Olanzapine (n=18) 1-20 mg/day Control 2: Quetiapine (n=18) 25-200 mg/day	80	Hospital, medical and surgical, mean age approx. 72y. Psychiatric liaison-service. Clinical observational study	In all groups the severity score (DRS) decreased. Poorer response in patients > 75 years	DSM-IV, DRS-R-98
Maneeton et al., 2013	Haloperidol (n=28) orally 0.5-2 mg/day vs quetiapine (n=24) orally 25-100 mg/day	52	RCT, double-blinded Medical patients Mean age 57	No significant differences in delirium severity (DRS-R-98) scores between groups.	CAM, DRS-R-98
Page et al., 2013	Haloperidol (n=71) iv 2.5 mg/8 h vs Placebo (n=70)	142	RCT, double-blinded Medical and surgical ICU patients needing mechanical ventilation included irrespective of delirium status. Mean age 68	Number of delirium-free and coma-free days were not significantly different between groups (median 5 vs 6 days, p=0.5)	CAM-ICU, RASS
Grover et al., 2011	Haloperidol (n=20) po/iv 1.25-2.5 mg, 2-3 doses/day vs. Olanzapine (n=23) po 1.25-20 mg/day vs. risperidone (n=21) po 0.25-4 mg/day	74	RCT, single-blind General hospital, medical and surgical wards referred to the liaison psychiatric team Age approx. 45 years, very few >65 years	Significant reduction in DRS-R98 in all groups (period 6 days), but no differences between groups	CAM, DRS-R-98
Kim et al., 2010	Risperidone (N=16) orally 0.25-2 mg/day, vs. Olanzapine (N=16) orally 1.25-7.5 mg/day	32	General hospital, medical and surgical, mean age approx. 67y	Improvements in both groups, no diff between groups. Poorer response of risperidone >70y.	DRS-R-98
Agar et al., 2016	Oral Risperidone (n=82) or Haloperidol (n=81) vs placebo (n=84), 0.5 mgx2, max 4mg/d for 72 hours	247	RCT, multicentre, palliative care, mean age approx. 75y	Reduced delirium distress symptoms at 72 h in placebo group vs risperidone (0.02) and haloperidol (0.009).	DSM-IV-R MDAS NuDESC
Cholinesterase inhibitors					
van Eijk et al., 2010	Rivastigmine (n=54) 1.5mg-6mg/12h vs. placebo (n=50) as an adjunct to usual care (haloperidol)	104	6 centres. RCT, placebo, double-blinded. ICU, mean age 69 +/- 12y Planned n=440	The trial was halted after 104 patients, because of a trend towards higher mortality (22% vs 8%, p=0.07) and longer duration of delirium (5 vs 3 days, p=0.06) in treatment group.	CAM-ICU
Overshott et al., 2010	Rivastigmine (n=8) 1.5 mg once daily (twice daily after 7 days) vs. placebo (n=7)	15	RCT, double-blinded, pilot study. Patients > 65 years with delirium admitted to medical wards	No significant differences in duration of delirium (6 days vs 10 days, p=0.5) Rivastigmine was well tolerated. Rivastigmine: 0/8 delirium after treatment. Placebo: 3/7 delirium-free after treatm.	CAM

Melatonin receptor agonists					
Clayton-Chubb and Lange, 2016 (ongoing)	Melatonin 5 mg vs placebo at 8 p.m. for 7 days		Medical patients >70 years planning 18 patients in each group	Ongoing study	CAM MDAS
Alpha-2 adrenoceptor agonists					
Rubino et al., 2010	Clonidine (n=15) iv 0.5ug/kg bolus, then cont. infusion 1-2 µg/kg/h vs placebo (n=15)	30	Postoperatively after AAA surgery, while on mechanically ventilation	Reduced severity of delirium in clonidine group	DSM-IV, Delirium Detection Score (DDS)
Carrasco et al., 2016	Dexmedetomidine (n=46) to patients who did not respond to haloperidol iv 2.5-5 mg (max dose 30 mg or RASS 0-minus 2) vs responders to haloperidol only (n=86).	132	Nonrandomized controlled. Non-intubated critically ill patients (medical-surgical ICU) diagnosed with agitated delirium (RASS+1 to +4)	Dexmedetomidine was an effective rescue drug when haloperidol failed	CAM-ICU, ICDSC
Reade et al., 2016	Dexmedetomidine (n=39) infusion 0.5ug/kg/t titrated to 0-1.5 µg/kg/h added to standard care vs placebo (n=32)	74	RCT, multicentre 15 ICUs Patients when extubation was inappropriate because of agitation or delirium. Median age 57years	The dexmedetomidine group had faster resolution of delirium (23 hours vs 40 hours, p=0.01 (a secondary outcome) and more ventilator-free hours at 7 days.	CAM-ICU
Li et al., 2017	Dexmedetomidine (n=142) vs placebo (n=143)	285	Double blinded RCT, 2 hospitals. Drug administrated during anesth and early postop phase after cardiac surgery	Dexmedetomidine did not reduced incidence of delirium Very low incidence (5-7%!)	CAM-ICU. RASS. MMSE
Other drugs					
Needham et al., 2016	Rosuvastatin 40 mg loading dose, then 20 mg x 1 vs placebo	272	Double-blinded placebo RCT, ancillary study.	No reduction of delirium and no less cognitive impairment at 12 month follow up with treatment	CAM-ICU

Figure 10. Flow diagram for patients screened at the acute geriatric ward for inclusion in LUCID

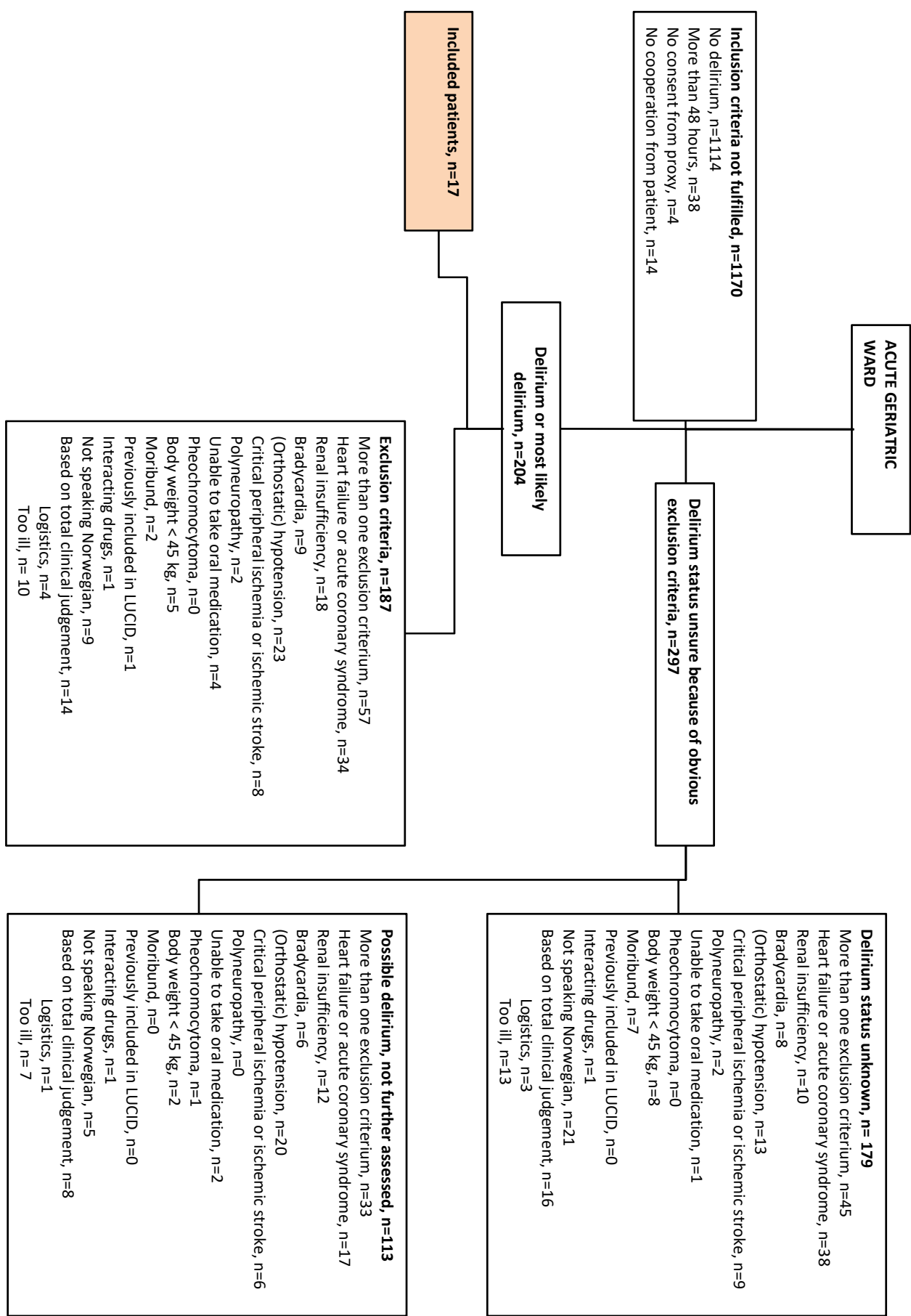


Figure 11. Flow diagram for patients screened at the acute medical observation unit for inclusion in LUCID

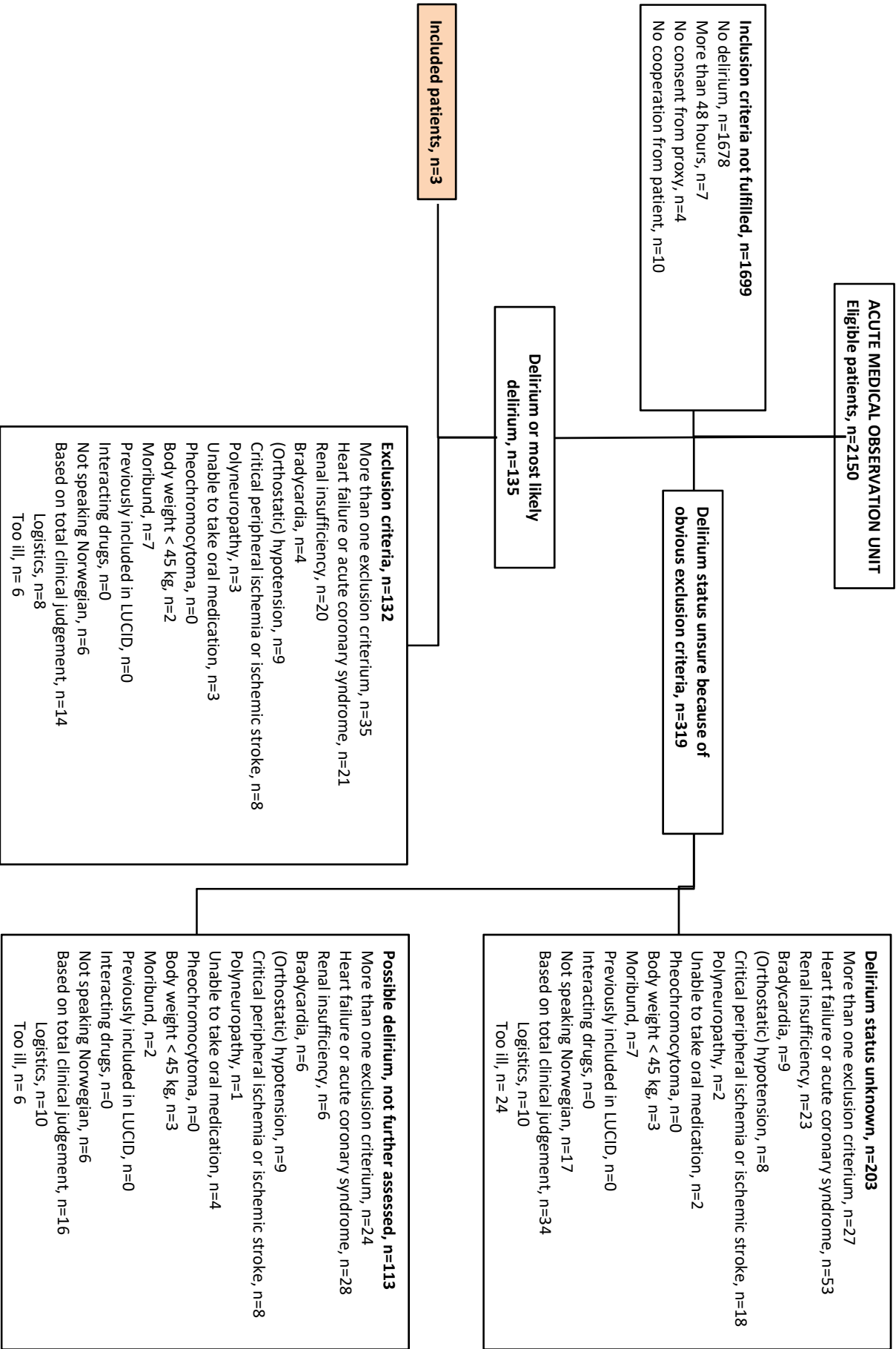


Figure 12. Flow diagram for patients screened at the general medical ward for inclusion in LUCID

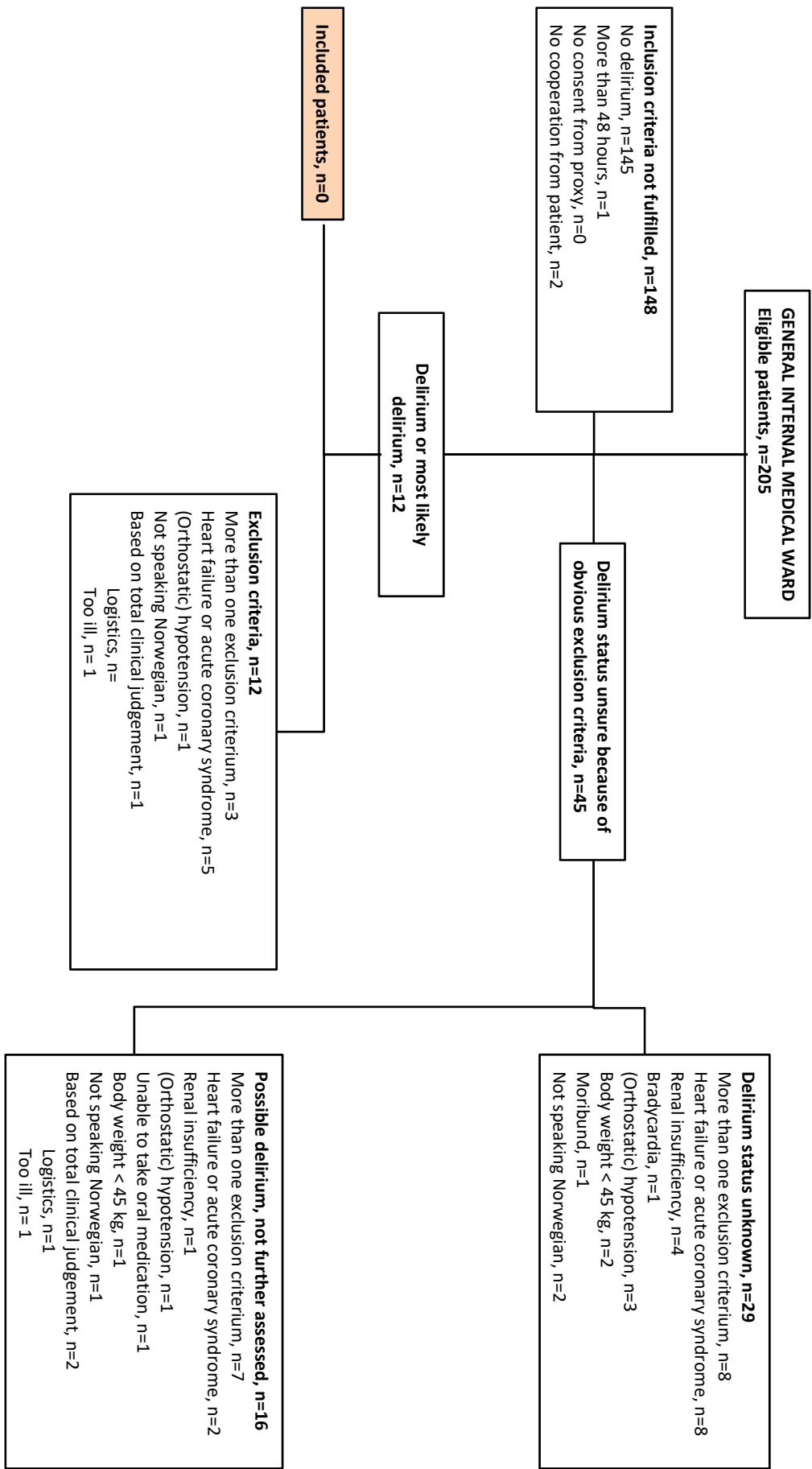
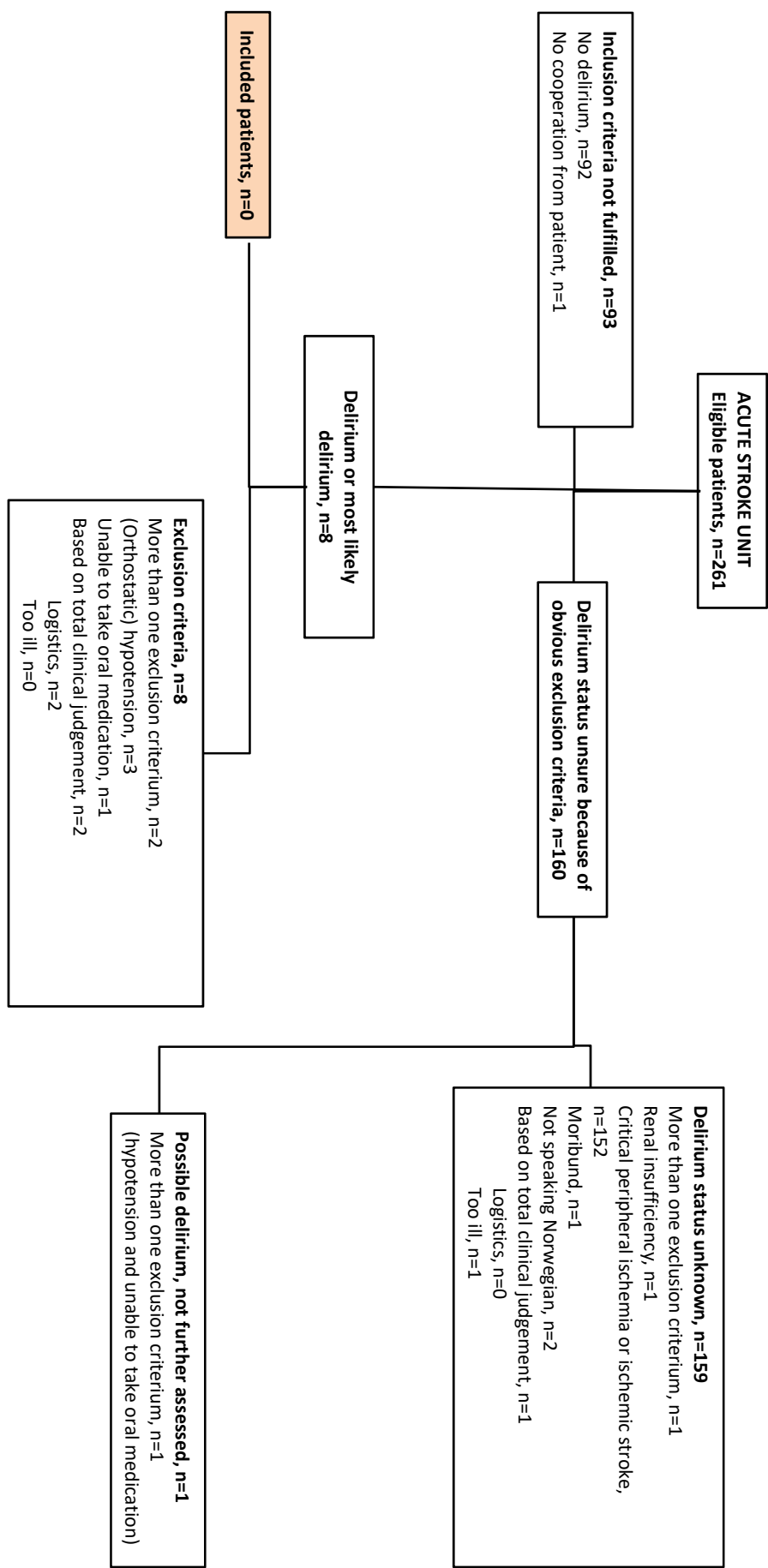


Figure 13. Flow diagram for patients screened at the acute stroke unit for inclusion in LUCID



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