Delirium after cardiac surgery
-risk factors, assessment methods and costs

Nina Smulter
To my family
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Abstract

Background
Cardiac surgery is considered safe, but postoperative delirium (POD) remains frequently reported. Delirium is characterised by fluctuations in consciousness and cognition, and can be subdivided into disturbed psychomotoric activity (hyperactive and hypoactive) and psychiatric symptom profiles (psychotic and emotional). Delirium has an underlying cause that can be prevented and treated, provided the condition is detected. Undetected delirium could lead to serious consequences for the patient.

Aim
This thesis aims to understand the underlying risk factors of delirium, to compare different assessment methods and documentation, and to understand its effects on hospitalisation costs after cardiac surgery.

Methods
Two cohorts of patients undergoing cardiac surgery at the Heart Centre, Umeå University Hospital, Sweden were analysed. Cohort-A (Studies I-IV) enrolled 142 patients, ≥70 years of age, scheduled in 2009 for surgery with cardiopulmonary bypass (CPB). POD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 4th ed, text rev (DSM-IV-TR), based on repetitive assessments with the Mini-Mental State Examination (MMSE) and the Organic Brain Syndrome (OBS) scale. This method was considered as reference. Predisposing and precipitating risk factors were explored (Study I), and a separate analysis was conducted with focus on CPB parameters (Study II). Patients were also assessed for POD with the Confusion Assessment Method (CAM), which was validated versus the reference method (Study III). Additionally in Study IV, data about how nurses assessed patients for POD symptoms using the Nursing Delirium Screening Scale (Nu-DESC) were analysed together with information extracted from the clinical database. Moreover, discharge summaries from both nurses and physicians were retrospectively reviewed for key words and expression associated with delirium. Cohort-B (Study V) included 1879 routine cardiac surgery patients (2014-2017) retrospectively extracted from the clinical database with concomitant Nu-DESC scoring. The association between the Nu-DESC and postoperative hospitalization costs was analysed.

Results
In cohort-A, 54.9% (78/142) patients developed POD. Both predisposing and precipitating risk factors were significantly associated with POD, of which the ‘volume load during operation’ had the strongest predictive influence (Study I). Among CPB variables the ‘duration of mixed-venous oxygen saturation <75%’
predicted POD (Study II). Hypoactive was more common than hyperactive delirium. Those with hypoactive delirium were less likely to be detected by the CAM method (Study III), an observation also demonstrated from information found in the clinical database and in discharge summaries. Nu-DESC did not detect all patients with POD, but significantly increased the detection rate (Study IV). The major hospitalisation costs associated with Nu-DESC ≥2 occurred in the ICU and independently of the surgical procedure performed. There were no significant differences in costs among patients with Nu-DESC ≥2, between age groups (70-year cut-off) or genders (Study V).

Conclusions
Both predisposing and precipitating risk factors contributed to POD and should be considered in future guidelines to prevent delirium after cardiac surgery. Hypoactive delirium was most common, but was the most difficult to detect without screening scales. Systematic assessment with Nu-DESC improved the detection rate of POD. Delirium after cardiac surgery has consequences on healthcare and is associated with increased costs.

Key words
Cardiac surgery, Cardiopulmonary bypass, Consequences, Delirium, Detection, Documentation, Economical aspect, Hospitalisation, Risk factors, Screening scales
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Grafting</td>
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<td>CAM</td>
<td>Confusion Assessment Method</td>
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<tr>
<td>CAM-ICU</td>
<td>Confusion Assessment Method for Intensive Care Unit</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<tr>
<td>CPB</td>
<td>Cardiopulmonary Bypass</td>
</tr>
<tr>
<td>CVD</td>
<td>Cerebrovascular Disease</td>
</tr>
<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders fourth Edition- Text Revision</td>
</tr>
<tr>
<td>I-ADL</td>
<td>Instrumental- Activities of Daily Living</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of Stay</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
</tr>
<tr>
<td>NRS pain</td>
<td>Numerical Rating Scale of pain</td>
</tr>
<tr>
<td>Nu-DESC</td>
<td>Nursing Delirium Screening Scale</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td></td>
<td>Functional Classification</td>
</tr>
<tr>
<td>OBS scale</td>
<td>Organic Brain Syndrome scale</td>
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<tr>
<td>P-ADL</td>
<td>Personal- Activities of Daily Living</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous Coronary Intervention</td>
</tr>
<tr>
<td>POD</td>
<td>Postoperative Delirium</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characteristic</td>
</tr>
<tr>
<td>S\textsubscript{v}O\textsubscript{2}</td>
<td>Mixed Venous Oxygen Saturation</td>
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**Sammanfattning på svenska**

**Bakgrund**
Hjärtkirurgi anses idag vara en säker metod men det förkommer frekventa rapporter om postoperativt delirium (POD). Delirium kännetecknas av fluktuationer i medvetandet och kognition och kan delas in i störd psykomotorisk aktivitet (hyperaktiva och hypoaktiva) och psykiatriska symtomprofiler (psykotiska och emotionella). Delirium har underliggande orsaker som kan förebyggas och behandlas, förutsatt att tillståndet upptäcks. Ett upptäckt delirium kan leda till allvarliga konsekvenser för patienten.

**Syfte**
Denna avhandling syftar till att förstå de underliggande riskfaktorerna för delirium, jämföra olika bedömningsmetoder och dokumentation samt förstå effekterna på vårdkostnaderna efter hjärtkirurgi.

**Metod**

**Resultat**
I kohort-A, utvecklade 54,9% (78/142) av patienterna POD. Både predisponerande och utlösande riskfaktorer var signifikant associerade med POD, varav ‘volymbelastningen under operation’ hade det starkaste prediktiva inflytandet (Studie I). Bland hjärt-lungmaskinens variabler bidrog ’duration av
blandad venös syremättnad <75’ till POD (Studie II). Hypoaktivt delirium var vanligare än hyperaktivt. Patienter med hypoaktiv delirium upptäcktes i mindre utsträckning med CAM (Studie III), en observation som också visade sig i information från den kliniska databasen och i epikriserna. Nu-DESC upptäckte inte alla patienter med POD men ökade detekteringsgraden signifikant (Studie IV). De största vårdkostnaderna i samband med Nu-DESC-poäng ≥2 inträffade på intensivvårdsavdelningen oberoende av kirurgiskt ingrepp som utförts. Det fanns inga signifikanta skillnader i kostnaderna mellan åldersgrupper (70-års brytpunkt) eller mellan män och kvinnor med Nu-DESC ≥2 (Studie V).

**Slutsatser**
Original publications


IV. Smulter N, Lingehall HC, Gustafson Y, Olofsson B, Engström KG. The use of a screening scale improves the recognition of delirium in older patients after cardiac surgery – a retrospective observational study. (Manuscript)

V. Smulter N, Hentschel J, Olofsson B Engström KG. The association between delirium symptoms according to the Nursing Delirium Screening Scale and hospitalization costs after cardiac surgery. (Manuscript)

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Background

Today, cardiac surgery is a common procedure, performed in a standardised way and considered safe with few complications. Consequently, cardiac procedures are now possible to perform in patients with severe comorbidity and a fragility burden, who were previously believed to be inoperable. However, this patient population is more prone to develop complications. Neurological side effects after cardiac surgery are common complications and remain a problem despite extensive research. Acute confusion is one of these, also described as postoperative delirium (POD).

Aspects of delirium

The patients’ perspective

The patients’ own experience of delirium varies widely. Some patients do not remember being delirious, whereas others describe the incidence clearly with feelings of anxiety, fear, and helplessness, being disorientated to place and time and hearing or seeing things that do not exist. These experience can be frightening, but also with neutral or enjoyable scenarios with a mixture of past and present events. One year after cardiac surgery, patients have described their experience as a scary complication with feelings of shame for their behaviour.

An episode of POD may involve an altered body perception, due to illusions and hallucinations. Lepoussé et al. (2006) described an increased mortality risk in these patients linked to self-harming, with examples of arterial and venous catheters being removed by the patient. Patients with delirium are more likely to have functional decline resulting in more fall injuries during the hospital stay with a continuing lack of independency in activities of daily living up to 6 months after surgery. In the long-term, POD is associated with an increased risk of stroke, increased hospital readmissions and a decrease in cognitive dysfunction, seen one year after cardiac surgery. Some of these patients may never recover to their baseline cognitive function. A cognitive decline after POD has been associated with a poorer quality of life and an increased long-term mortality risk after cardiac surgery.

The nursing perspective

With their ongoing contact with the patient in clinical care, nurses are in the best position to recognise delirium symptoms. However, the syndrome remains under-recognised by nurses. In a busy hospital environment, delirium is
challenging to detect. Poor knowledge about delirium and the lack of screening scales may be reasons behind this challenge. It has been reported that screening scales are mostly used for those patients that present a ‘suspicious behaviour’ with agitation, restlessness, etc. Caring for a delirious patient has also been described by the nurses to cause stress in the working situation, with an emotional challenge, including frustration and physical exhaustion. Some nurses even feel uncomfortable in caring for delirious patients, due to distrust, irritable and sometimes violent behaviours. Communication with these patients can be meticulous with a feeling of ineffectiveness.

Nurses have reported that they lack knowledge about delirium symptoms and how to manage these, which can be a barrier in the care of delirious patients. Moreover, a communication gap between professionals has been described, with co-operation lacking between physicians and nurses. Generally, there may be a lack of time, resources and opportunities to discuss and initiate a care plan within the team around the patient, and the care of these patients often requires more staff members. It has been described that the extra workload generated by a delirious patient is rarely taken into account and the nurses feel that they do not get the required support from their immediate supervisors.

The surgical perspective

POD after cardiac surgery is associated with complications for the patient both in the early postoperative period, but also in the long-term perspective. Delirium in general is known to increase the risk of complications including aspiration, pressure ulcers, pulmonary emboli and decreased oral intake. POD was early identified as a complication to cardiac surgery, and brain protection has been an ongoing concern since the early days of surgery with cardiopulmonary bypass (CPB). The association between CPB and delirium directed the attention to oxygenator technology and wound-blood recycling. The condition was described as "post-cardiotomy delirium". Nevertheless, POD is also observed among patients who have not been exposed to CPB, undergoing general or orthopaedic surgery. Moreover, delirium is a psychiatric term regardless of surgery, and occurs also in non-surgery medical patients. The incidence of delirium varies between the different patient groups. Among medical inpatients the incidence varies between 10 and 31%, while after orthopaedic surgery incident rates of 62% to 75% have been reported. Patients undergoing cardiac surgery with CPB belong to a group with a high reported incidence of POD, between 23% and 72%.
Delirium characteristics

Delirium might be the first symptom of an underlying disease or a side effect of a medical treatment. Older patients are at greater risk of POD, which may be explained by age-related changes in the brain. Atherosclerosis is more common among older patients, and the risk for neurological dysfunction increases. For patients admitted for cardiac surgery, atherosclerotic vascular disease might contribute to organ dysfunction, and cognitive- and functional impairment, which places these patients at an increased risk of developing POD.

Delirium is a neuropsychiatric syndrome characterised by a disturbed consciousness accompanied with a change in cognition. It develops gradually within hours or days and fluctuates in course. Delirium varies in its psychomotoric activity, with a subdivision into hyperactive, hypoactive and mixed hyper- and hypoactive forms. Clinical signs of hyperactive delirium include irritability, violence, restlessness, euphoria and anger. The hypoactive state of delirium is exemplified by ignorance, lethargy, staring and stupor. Disturbances in the sleep-wake cycle are symptoms that may be associated with delirium. Delirium may also be subdivided into its psychiatric symptom profiles, separating those with psychotic symptoms versus emotional symptoms. Examples of psychotic symptoms are hallucinations, paranoia or illusions, and emotional symptoms which include depressed mood, emotional lability and anxiety.

The delirious subtypes differ in terms of causality, detection, treatment and prognosis. A state of hyperactive delirium may alert health care professionals to respond. This may not be the case with hypoactive delirium in which the delirious condition has more subtle symptoms. Hypoactive symptoms are more common in older patients, and these symptoms may also be associated with dementia. It has been reported that patients with hypoactive delirium are subject to more postoperative complications than non-delirious patients.

Detection and documentation of delirium

It has been suggested that screening scales are necessary for health care professionals to correctly detect POD. This was confirmed in the study by Eriksson et al. (2002), showing that both nurses and physicians had difficulties detecting POD after cardiac surgery. Of the 52 included patients 12 developed POD, but none of these patients were correctly identified in the clinical database by the nursing staff or physicians. Clinical databases are commonly used in daily clinical care as well as for research purposes. These databases are considered valuable in order to increase the quality of health care.
in the study by Åberg and Hentschel (2004), investigating the predictive strength of recorded factors, including delirium, for their influence on the outcome after cardiac surgery. The database was suggested to be a powerful instrument for the monitoring of quality and to follow changes in clinical practice.  

Delirium assessment methods have mainly been designed for research purposes, often being extensive and time consuming and therefore difficult to use in daily care. With the ambition of making delirium assessments more manageable in clinical practice, various instruments have been proposed for screening of delirium, for example, the Confusion Assessment Method (CAM) and the Nursing Delirium Screening Scale (Nu-DESC). The CAM is the most commonly used screening instrument for delirium in both clinical care and research. The CAM was developed by Inouye et al. in 1990, as an observational instrument which was quick to use by nurses and requiring minimal interviewing. The Nu-DESC was developed by Gaudreau and colleagues in 2005 with a similar ambition of an easy-to-use screening instrument for nurses. The Nu-DESC has been suggested to have a good sensitivity in different health care settings, for example, in the recovery room, surgical ward, intensive care unit, and in the geriatric ward. Nu-DESC has been translated into Swedish and has been validated among patients undergoing cardiac surgery.

Documentation is an important and essential part of patient care. Shaughnessy (2013) showed that less than 50% of the patients expressing delirium after cardiac surgery were documented in the medical records by nurses and physicians when discharged from the Intensive Care Unit (ICU) to the care unit. Patients discharged from the hospital without a correct diagnosis of delirium can lead to serious consequences in that established nursing and medical care routines for these patients are not followed. Conversely, treatment with delirium-confounding drugs may continue on the receiving unit in patient without this need, causing ward-related complications of drug overuse.

Risk factors for POD

By its definition POD is reliant on the underlying mechanisms to develop. Numerous risk factors for delirium have been described in the literature, pointing towards the multifactorial characteristics of POD. These are divided into predisposing and precipitating risk factors. Predisposing factors are conceptualised as those present upon admission to hospital. Among these, a reduced brain reserve capacity may cause the patient to be more susceptible to POD. Precipitating factors are those that develop during the period of hospitalisation, exemplified by negative effects from surgical and medical treatment. An important step in order to prevent delirium is to increase the
knowledge of both predisposing and precipitating risk factors. Examples of known predisposing factors are advanced age, male gender, visual impairment, reduced functional ability, sleep deprivation, depression and cognitive impairment. Examples of precipitating factors are infections, nutrient shortage, anaemia, hypoxia, constipation, pain, and various side effects of drugs. In cardiac surgery, CPB is considered a key contributor to POD. Bucereus and colleagues (2004) suggested that cardiac surgery without the use of CPB may lead to a lower incidence of POD. There are additional studies indicating that patients undergoing cardiac surgery with CPB have an increased risk of delirium. Aortic manipulation associated with CPB cannulation and clamping may dislodge particles causing cerebral complications due to both macro- and/or microembolisation. Lipid microemboli from retrieved mediastinal blood that enters the arterial CPB circuit is another concern regarding brain injury. Moreover, haemodynamic fluctuations may cause cerebral hypoxia, not limited to the period of CPB, but also after CPB weaning. Overall, the artificial nature of CPB may hide several mechanisms of brain injury with relevance to POD. There still remains a lack of complete understanding within this field of science.

Economic consequences of POD

In recent years, increased attention has been paid to the negative effects of delirium on hospital costs and on postoperative outcomes, including long-term survival and hospital readmission. Other consequences associated with POD have also been noticed, such as impaired health status and quality of life. In the ICU, patients with POD require a longer period of respiratory support than those without this syndrome and with an overall longer need of ICU stay. Similarly in the general ward, patients with POD show a prolonged hospitalisation period, and at discharge, they are more often referred to a nursing home placement than to their home.

Rationale

POD is a common complication to cardiac surgery, with obvious negative consequences for the patient, medical ward and economy. Delirium has an underlying cause that can be prevented and treated. Therefore, identifying risk factors becomes of crucial importance and needs further investigation. To accomplish these goals delirium must be correctly detected and documented. Screening instruments may offer a reasonable compromise between diagnostic accuracy and daily-care simplicity. This project addresses POD, in terms of risk factors, assessment methods and economic consequences.
Aim
The overall aim of this thesis is to explore the underlying risk factors of delirium, to compare different assessment methods and documentation, and to better understand the effect of delirium on hospitalisation costs after cardiac surgery.

Specific aims for each study

- To explore risk factors behind POD in older patients undergoing cardiac surgery with CPB (Study I).

- To explore risk factors behind POD, specifically associated with the conduct of CPB (Study II).

- To evaluate the congruent validity of the CAM versus the DSM-IV-TR criteria of delirium, as repeatedly assessed by the OBS scale and the MMSE (Study III).

- To analyse POD in clinical practice after cardiac surgery, how it is detected and documented and if the use of a screening scale may improve the detection rate (Study IV).

- To analyse the association between delirium symptoms according to the Nu-DESC and costs of hospitalisation after cardiac surgery (Study V).
Methods

This thesis is based on two patient cohorts, both operated upon at the Cardiothoracic Surgery Department, Heart Centre, Umeå University Hospital, Sweden. Table 1, shows an overview of the studies on which this thesis is based.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of inclusion</th>
<th>Patients</th>
<th>Data character</th>
<th>Analyses</th>
<th>Status and Publication</th>
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<tr>
<td>I</td>
<td>2009</td>
<td>Cohort-A (n = 142)</td>
<td>Prospective observational study</td>
<td>Risk-factor analysis of predisposing and precipitating variables</td>
<td>Published 2013 in Interact Cardiovasc Thorac Surg</td>
</tr>
<tr>
<td>II</td>
<td>2009</td>
<td>Cohort-A (n = 142)</td>
<td>Prospective observational study</td>
<td>Risk-factor analysis with specific focus on CPB technology</td>
<td>Published 2017 in J Cardiothorac Vasc Anesth</td>
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<td>Prospective observational study</td>
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<td>Published 2015 in Am J Crit Care</td>
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<td>IV</td>
<td>2009</td>
<td>Cohort-A (n = 78)</td>
<td>Retrospective observational study</td>
<td>Quantitative Descriptive statistics</td>
<td>Manuscript</td>
</tr>
<tr>
<td>V</td>
<td>2014-2017</td>
<td>Cohort-B (n = 1879)</td>
<td>Retrospective observational study</td>
<td>Quantitative Descriptive statistics</td>
<td>Manuscript</td>
</tr>
</tbody>
</table>

Ethical approval

Cohort-A: Prior to surgery patients received both oral and written information about the study and asked to participate. The patients could withdraw from further participation at any time without needing to give reasons. Participation did not interfere with either surgery or clinical care. Cohort-B: Data were retrospectively extracted from the clinical database.

The results from all studies were aggregated on a group level and individuals are unable to be identified. This thesis followed ethical principles of the Declaration of Helsinki. The studies were approved by the ethics review board at Umeå University, studies I-IV Dnr 08-169M and Study V Dnr 2015/422-31, respectively.
Cohorts and settings

Cohort-A (Studies I-IV)

Patients ≥70 years of age undergoing routine cardiac surgery with CPB were prospectively enrolled in 2009 (February to October). During the study period, 199 patients were admitted to the unit and were potential for inclusion. The exclusion criteria were acute operation within 24 hours from admission, planned deep hypothermic arrest, serious psychiatric disease, severe communication difficulties and severe vision or hearing problems. Six of the 199 patients met the exclusion criteria and 15 were lost for administrative reasons leaving 178 subjects who were asked to participate in the study. A total of 153 patients gave oral and written consent to participate. Due to various reasons eleven patients did not complete the study protocol and were therefore excluded, leaving 142 patients for the analyses (Figure 1). The 36 excluded patient did not differ in terms of gender, age and surgical procedures.

In Study III, one patient had not completed the Confusion Assessment Method (CAM) assessment, leaving 141 patients for analysis. Study IV focused on the 78 patients diagnosed with POD among the 142 patients in cohort-A.
Figure 1. Flow chart of inclusion process of participants in cohort—A

199 patients ≥70 years of age scheduled for routine cardiac surgery during the study period
71 women, 128 men

178 patients invited to participate in the study
63 women, 115 men

11 patients did not fulfil the study protocol due to:
3 no surgery, 1 postoperative stroke, 5 intubated postoperatively, 2 missing data

153 patients included
56 women, 97 men

142 patients analysed in Studies I and II
50 women, 92 men

11 patients did not fulfil the study protocol due to:
3 no surgery, 1 postoperative stroke, 5 intubated postoperatively, 2 missing data

25 declined
7 women, 18 men

141 patients analysed in Study III
50 women, 91 men

64 patients without POD excluded
26 women, 38 men

78 patients analysed in Study IV
24 women, 54 men

21 patients excluded due to:
5 acute surgery, 1 not fluent in Swedish, 15 logistical reasons

141 patients analysed in Study III
50 women, 91 men

1 patient did not complete the CAM protocol

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26 women, 38 men

78 patients analysed in Study IV
24 women, 54 men

21 patients excluded due to:
5 acute surgery, 1 not fluent in Swedish, 15 logistical reasons

141 patients analysed in Study III
50 women, 91 men

1 patient did not complete the CAM protocol
**Cohort-B (Study V)**

Patients undergoing cardiac surgery with CPB between May 19\textsuperscript{th} 2014 and March 30\textsuperscript{th} 2017 (n=1947) were retrospectively extracted from the clinical database at the Cardiothoracic Surgery Unit. Exclusion criteria were those patients missing Nu-DESC registration and/or a period of hospitalisation shorter than 3 days. Sixty-eight patients were rejected leaving 1879 patients for the analyses (Figure 2). The excluded patients did not differ from those included in terms of age and gender.

**Figure 2. Flow chart of inclusion process of participants in cohort-B**

The two cohorts had a liberal inclusion of different open heart surgical procedures all sharing CPB. The procedures included coronary artery bypass grafting (CABG), valvular surgery isolated or combined and procedures involving the ascending and descending aorta.
Data collection

Cohort-A (Studies I-IV)

Demographic details of cohort-A (Studies I-IV) are shown in Table 2. For cohort-A, a comprehensive protocol was designed to collect surgical and ward-related variables that prospectively followed each patient through the hospitalisation period; pre-, intra- and postoperatively. In addition to these manually recorded variables, demographic and surgery related details were extracted from the clinical database. Results from laboratory blood tests were extracted from the patient records.

For the diagnosis of POD of cohort-A patients, a structured face to face interview was conducted using different assessment scales. The interviews lasted approximately 25-45 minutes. The first interview took place ahead of surgery, typically on the ward. The second interview occurred on postoperatively day 1 (+1) in the ICU or in the step-down unit. The third and last interview, on day 4 (±1), typically occurred on the ward, but in some cases in the step-down unit or in the ICU.

For Study IV discharge summaries of the 78 patients with POD were retrospectively reviewed to extract information about the ability of nurses and physicians to detect and document POD at discharge. Also, the daily patient notes were reviewed to collect information about the Nu-DESC scoring registered by the nurses on the unit.
### Table 2. Baseline characteristic for cohort-A (n=142)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>76.6 ± 4.4</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>92 (64.8)</td>
</tr>
<tr>
<td>Females</td>
<td>50 (35.2)</td>
</tr>
<tr>
<td>MMSE (score)</td>
<td>27.0 ± 2.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.1 ± 9.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.7 ± 13.5</td>
</tr>
<tr>
<td>I-ADL (dependent)</td>
<td>55 (38.7)</td>
</tr>
<tr>
<td>P-ADL (dependent)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23 (16.2)</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>17 (12.0)</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>CVD</td>
<td>21 (14.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>17 (12.0)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>31 (21.8)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>57 (40.1)</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>99 (69.7)</td>
</tr>
<tr>
<td>Unstable</td>
<td>42 (29.6)</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>96 (67.6)</td>
</tr>
<tr>
<td>Mild</td>
<td>20 (14.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>24 (16.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td>Class II</td>
<td>33 (23.2)</td>
</tr>
<tr>
<td>Class III</td>
<td>79 (55.6)</td>
</tr>
<tr>
<td>Class IV</td>
<td>25 (17.6)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>21 (14.8)</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>8 (5.6)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>CABG isolated</td>
<td>85 (59.9)</td>
</tr>
<tr>
<td>Valves isolated</td>
<td>28 (19.7)</td>
</tr>
<tr>
<td>Combined procedures</td>
<td>29 (20.4)</td>
</tr>
</tbody>
</table>

Abbreviations: CABG, coronary artery bypass grafting; Combined procedures, coronary artery grafting (CABG) and valve replacement/repair; CVD, cerebrovascular disease; I-ADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; NYHA, New York heart association functional classification; P-ADL, personal activities of daily living; PCI, percutaneous coronary intervention
Cohort-B (Study V)

For cohort-B, demographics and surgical details were retrospectively extracted from the clinical database. Demographic details for cohort-B are presented in Table 3. Costs associated with hospitalisation were based on the length-of-stay (LOS) in the ICU and on the ward. In these calculations only the postoperative period was considered. Information about LOS costs in the ICU and ward, respectively, was obtained from the hospital’s accounting department. This describes the standardised charging costs, which take into account staff density, drugs, facilities and administrative overhead costs. The costs increased each year, and in order to simplify, mean values were calculated for the three years of patient inclusion.
### Table 3. Baseline characteristic for cohort-B (n=1879)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (Q₁; Q₃)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.3 (61.7; 75.5)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1381 (73.5)</td>
</tr>
<tr>
<td>Females</td>
<td>498 (26.5)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.0 (167.0; 180.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.0 (73.0; 92.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>428 (22.8)</td>
</tr>
<tr>
<td>COPD</td>
<td>109 (5.8)</td>
</tr>
<tr>
<td>CVD</td>
<td>152 (8.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1369 (72.9)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>273 (14.5)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>328 (17.5)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>546 (29.1)</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>725 (38.7)</td>
</tr>
<tr>
<td>Class I</td>
<td>151 (8.0)</td>
</tr>
<tr>
<td>Class II</td>
<td>333 (17.7)</td>
</tr>
<tr>
<td>Class III</td>
<td>494 (26.3)</td>
</tr>
<tr>
<td>Class IV</td>
<td>172 (9.2)</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1385 (73.7)</td>
</tr>
<tr>
<td>Mild</td>
<td>235 (12.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>190 (10.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>69 (3.7)</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>369 (19.6)</td>
</tr>
<tr>
<td>Class II</td>
<td>600 (31.9)</td>
</tr>
<tr>
<td>Class III</td>
<td>758 (40.3)</td>
</tr>
<tr>
<td>Class IV</td>
<td>152 (8.1)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>216 (11.5)</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>87 (4.6)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>Isolated</td>
<td>1425 (75.8)</td>
</tr>
<tr>
<td>Combined</td>
<td>260 (13.8)</td>
</tr>
<tr>
<td>Vascular</td>
<td>194 (10.3)</td>
</tr>
</tbody>
</table>

Abbreviations: Angina, the Canadian Cardiovascular Society (CCS) classification of angina pectoris; CABG, coronary artery bypass grafting; Combined, coronary artery grafting (CABG) and valve replacement/repair; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; Isolated, CABG or valve replacement/repair; NYHA, New York heart association functional classification; PCI, percutaneous coronary intervention; Vascular, procedures involving the ascending, arch and/or descending aorta.
Assessment scales

An overview of the assessment scales used in the studies included in this thesis are presented in Table 4.

Table 4. Assessment scales and POD registry used in this thesis

<table>
<thead>
<tr>
<th>Assessment scales</th>
<th>Cohort Study</th>
<th>A</th>
<th>A</th>
<th>A</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Mental State Examination (MMSE)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic Brain Syndrome scale (OBS)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katz Index scale of Independence in Activities of Daily Living (Katz-ADL)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Confusion Assessment Method (CAM)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing Delirium Screening Scale (Nu-DESC)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical database</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Mini-Mental State Examination

In cohort-A, the Mini Mental State Examination (MMSE) was used to evaluate the patient’s cognitive status pre- and postoperatively. The MMSE was developed by Folstein et al. in 1975 as an instrument to assess cognitive impairment.\(^{80}\) The instrument can also be used to estimate the progression and severity of cognitive impairment and to follow cognitive impairment over time.\(^{81}\) The MMSE consists of two parts with 11 tasks. The first part addresses attention, memory and orientation. The second part addresses the ability to respond to verbal or written information.\(^{80}\) The MMSE has a score of 0-30, with a suggested cut-off at 24 to indicate cognitive impairment.\(^{80,81}\) In the present reports and thesis the MMSE replaced the first part of the OBS scale (see below).

The Organic Brain Syndrome Scale

The Organic Brain Syndrome (OBS) scale was developed to assess various psychiatric conditions such as perceptual, emotional, psychotic symptoms and is also sensitive to fluctuations over time.\(^{82-84}\) The OBS scale consists of two parts, a disorientation and a confusion subscale. The disorientation subscale is a questionnaire with 15 items measuring the patient’s orientation to time, place and own identity. The confusion subscale contains items describing cognitive,
emotional, perceptual and personal changes and fluctuations. The second part of the OBS scale is based on interviews and observation of the patient, but also interviews with the caregivers.\textsuperscript{82,83} Each item in the OBS scale is rated from 0 to 3, with 0 indicating no symptoms and 3 indicating significant symptoms.\textsuperscript{84} Moreover, the OBS scale allows delirium to be divided into different subtypes of psychomotor activity (hyper-, hypo-, and mixed delirium) and psychiatric symptom profiles (emotional, psychotic, and mixed emotional and psychotic symptoms).

In the present reports, a modified version of the OBS scale was used, with the first part evaluating cognitive status being replaced by the MMSE scale. The combination of MMSE and OBS scale has been used among research professionals to detect delirium in several previous studies and for a variety of patients,\textsuperscript{34,44,45,85} and this combination is considered to have a good concurrent validity and effectiveness.\textsuperscript{34,82,84} The second part of the OBS scale covers 39 items of which 34 were used and evaluated; the remaining items were replaced by the Katz Staircase, including the Katz ADL index.

**Katz Staircase, including the Katz ADL index**

The patient’s functional status in performing Active of Daily Living (ADL) was assessed by using the Katz Staircase, including the Katz ADL index.\textsuperscript{86,87} This scale includes both Personal-ADL (P-ADL), which takes in to account bathing, dressing, transfer, continence and feeding, but also Instrumental-ADL (I-ADL), which includes cleaning, shopping, transportation and cooking. In this thesis, 5 items of the OBS scale regarding ADL were replaced by the Katz Staircase, including the Katz ADL index. (Studies I-IV) In Study III, I-ADL and P-ADL were assigned and dichotomised to independent or dependent.

**The Confusion Assessment Method**

The Confusion Assessment Method (CAM) was introduced in 1990 by Inouye et al. as an easy-to-use screening instrument to improve the detection of delirium.\textsuperscript{56} The CAM is a widely used and standardised delirium instrument for both clinical and research purposes and has been translated into several languages and validated in various care settings.\textsuperscript{88} The CAM is based on *Diagnostic and Statistical Manual of Mental Disorders, 3\textsuperscript{rd} edition revised* (DSM-III-R) criteria and includes nine clinical features; acute onset and fluctuating course, inattention, disorganised thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbance, increased or reduced psychomotor activity, and disturbance in the sleep-wake
cycle. A diagnosis of delirium according to the CAM algorithm requires the presence of both the first and second item together with a positive observation of either the third and/or fourth item.\textsuperscript{56} The English version of the CAM was used in Study III because there was no validated version of the scale in Swedish available at the time.

**The Nursing Delirium Screening Scale**

The Nursing Delirium Screening Scale (Nu-DESC) was designed as an easy-to-use instrument for the detection of delirium symptoms in daily clinical care.\textsuperscript{89} The scale is not considered a diagnostic instrument, instead it is designed for screening. The Nu-DESC consists of five domains; disorientation, inappropriate behaviour, inappropriate communication, illusions or hallucination and psychomotor retardation. Each item is graded from 0 to 2 to reflect the magnitude of symptoms, and with the five items together the maximum score is 10. The scoring is repeated over time by the nurses caring for the patient, typically after the work shift, and thus three times per day. A Nu-DESC score of ≥2 points is suggested to indicate delirium.\textsuperscript{57}

Prior to the study period in 2009, nurses on the Cardiothoracic Surgery Unit received a one hour lecture about delirium and how to use the Nu-DESC by two experts in the field.\textsuperscript{49} In Study IV the Swedish version of Nu-DESC was used and compared with different methods to detect and document POD in daily clinical practice. The Nu-DESC was introduced 2009 for research purposes in cohort-A, to become screening routine at the Cardiothoracic Surgery Unit and to be recorded in the clinical database, starting in 2013. The Nu-DESC was further analysed in Study V.

**Clinical database**

The Cardiothoracic Surgery Department at the Heart Centre of Umeå University Hospital has a long tradition of both designing and using clinical databases.\textsuperscript{51} Apart from collecting data, the present database is an administrative tool for the patient referral process, for operation programme planning, and for extracting and delivering data to the Swedish National Heart Disease Registry (SWEDEHEART).\textsuperscript{90} In the present studies and thesis, a subset of relevant pre-, intra-, and postoperative data were extracted. The database has been described in several previous reports and is considered to be a useful and accurate instrument for the registration of complications and a source for improvement of clinical routines and treatments.\textsuperscript{53,91} This database is shared between four of the eight Cardiothoracic Surgery Units in Sweden.
The clinical database includes a variable called “Confusion” with the associated definition “delirium that affects patient mobilisation”. This variable was recorded at patient discharge and referred to observations made by nurses and physicians during the patients’ hospital stay. The variable does not rely upon standardised diagnostic criteria or use of screening tools. The clinical database is considered here as a registry for documentation of delirium (Study IV).

**Study procedures**

*Delirium diagnosis*

In cohort-A the POD diagnosis relied on the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision* (DSM-IV-TR), by which MMSE and OBS scale observations were evaluated. The POD diagnosis was set by two experienced researchers (one physician and one nurse) in geriatric medicine after the patient was discharge. The procedure consisted of four steps. Initially and independently between the two researchers, the MMSE scorings were evaluated, and in the second step the OBS scale, which was followed by a third step of a combined analysis of the MMSE and the OBS scale. Finally in the fourth step, the two researchers discussed each patient towards a consensus of POD diagnosis. This diagnostic process is referred to here as reference method in Studies I-IV.

In cohort-B, the Nu-DESC scoring was evaluated and used as an instrument indicating delirium symptoms. As previously suggested a score of two or higher was considered as an indicator of POD. However, this measure is not a POD diagnosis.

*Study designs*

In studies I-II, potential risk factors contributing to delirium after cardiac surgery for cohort-A were analysed. In Study I, an extensive list of variables was generated and considered for analysis. For condensation purposes, these were subdivided into predisposing and precipitating variables. Predisposing variables were those known in advance of surgery, whereas precipitating factors were those the patient became exposed to during and after surgery. In Study I, CPB variables were only briefly addressed. The CPB procedure holds in itself an extensive number of technical and laboratory details that can be digitally extracted from the CPB specific database. These data were extracted separately. Both timing and the surplus of existing variables for Study I resulted in a separate Study II with specific focus on CPB and on those variables available for the perfusionist to control. With this knowledge, the perfusionist can tune the CPB in order to avoid exposures to factors that might contribute to POD development.
In Study III, the CAM screening scale was validated versus the reference diagnosis within cohort-A. The CAM is unable to discriminate between delirium subtypes, as given by the reference method. Nevertheless, this allowed for validation of the CAM performance to correctly identify delirium in these subtype groups. Moreover, the CAM instrument was repeated on day 1 and day 4 postoperatively, synchronically with the reference method, by which a temporal comparison between the two methods was available.

Study IV was designed to compare the ability of detecting POD and POD-related symptoms in clinical practice after cardiac surgery, with and without the support of a screening instrument. During the study period of cohort-A, different methods to detect and document delirium were reviewed and analysed; registration of POD in the clinical database, documentation of POD in discharge summaries by nurses and physicians, and daily Nu-DESC assessments of delirium symptoms by the nurse in charge of the patient. A comparison was made against the reference diagnosis for POD. A comparison was also made between the identification rate following Nu-DESC screening and that recorded in the clinical database. Moreover, key words and expressions sensitive to delirium were extracted from discharge summaries of the 78 patients diagnosed with POD. Summaries from both nurses and physicians were reviewed in this way, and key words and expressions were selected as previously suggested in the literature.93-94

In Study V and cohort-B the Nu-DESC screening for POD symptoms was retrospectively analysed. A Nu-DESC score of two or more was considered as a delirium symptom and the study population was grouped into Nu-DESC ≥2 or Nu-DESC <2. The accumulated hospitalisation costs were differentiated for surgery subtypes, gender and age.

**Data analyses**

**Quantitative analyses**

Generally, continuous variables were checked for normal distribution by means of the Shapiro-Wilk’s test, followed by analysis of intergroup differences by the Student t-test, or otherwise, by the Mann-Whitney U-test. Categorical variables were cross-tabulated and differences were tested by Chi-square or Fisher's Exact test.

In Study I univariate regressions were used to estimate the association between the independent factors (predisposing and precipitating risk factors) and POD as a dependent factor. Variables with a p-value below 0.10 were selected as potential predictors of POD and entered into a multivariable logistic regression model in
both study I and II, with a backward approach. The predictive strength of the different models was presented in a receiver operating characteristic (ROC) curve in both study I and II.

In this thesis the two sets of data from Studies I and II were merged into a multivariable logistic regression. The two studies shared the predisposing variables, and only the precipitating variables had relevance for merging, by incorporating the CPB-specific variables from Study II to Study I. In a second step, the predisposing variables were added to the multivariable analysis. Variables univariately associated with POD at p-value of <0.10 were introduced for multivariable analysis in a similar fashion as described for Study I. Covariates were avoided, and the variable volume load during surgery in Study I was preferred instead of the CPB fluid balance used in Study II. Similarly, the preoperative weight was used rather than BSA in Study II where the algorithm includes weight. Also, the time of surgery in Study I, which includes CPB time was used rather than the CPB time only.

In Studies III and IV cross-table comparison of different assessment methods to detect and document POD were analysed by McNemar binomial testing. Specificity and sensitivity against the diagnostic reference were calculated for relevant comparisons.

In Study V, the association between Nu-DESC scores and postoperative hospitalisation costs between surgery subtypes, age groups (70-year cut-off) or gender were analysed. Surplus costs between the Nu-DESC groups were calculated on the basis of the differences in total hospitalisation costs for the different surgical procedures.

**Quantitative content analysis**

In Study IV, quantitative content analysis was used to systematically analyse the key words and expressions extracted from the discharge summaries. The analysis consisted of several steps, beginning with the identification of the material intended for analysis versus raised questions of research. The following step of analysis is to determine a coding scheme that provides classification rules for the extracted coding units to specific categories or concepts.\(^{95,96}\) The five items from the Nu-DESC; disorientation, inappropriate behaviour, inappropriate communication, illusions and hallucinations, and psychomotor retardation were used here as a coding scheme. The classification of the key words and expressions into the five items were inspired by the definitions given by Gaudreau et al. (2005).\(^{57}\) During the classification process, key words and expressions extracted from the discharge summary were reviewed together in the research group to
reach consensus. In the last step of the quantitative content analysis the coding units can be transformed into 0 and 1 to analyse with descriptive statistics, which was done in Study IV.
Results

Main results from each study are collectively presented here.

POD incidence and symptom profiles

In cohort-A, 54.9% (78/142) were diagnosed with delirium according to the reference method. POD was classified into two groups of psychomotor activity and psychiatric symptom profiles. In psychomotor activity, 58.9% (46/78) of the patients were classified as hypoactive, 23.1% (18/78) hyperactive or mixed, whereas 17.9% (14/78) were considered non-classifiable. In psychiatric symptom profiles, 21.8% (17/78) of the patients had an emotional symptom profile, 14.1% (11/78) psychotic symptoms, 32.1% (25/78) mixed emotional/psychotic symptoms and 32.1% (25/78) were considered non-classifiable (Studies I-IV). These subgroups are further explored in Study III and IV.

In cohort-B, of the 1879 analysed patients in Study V, 20.1% (377/1879) had delirium symptoms recorded as a Nu-DESC score ≥2. The incidence of POD cannot be concluded because the Nu-DESC only assesses symptoms. Delirium subtypes of psychomotor activity or psychiatric symptoms were also unable to be described by the Nu-DESC.

POD risk factors after cardiac surgery

In Study I, data of the 142 patients from cohort-A were analysed to identify risk factors of POD. The multivariable logistic regressions were conducted in two steps, first separately for predisposing and precipitating factors, respectively, and then merged. Among predisposing factors ‘Numerical Rating Scale (NRS) of pain’, ‘diabetes’, ‘preoperative oxygen saturation’ and ‘combined surgical procedures’ were identified. Among precipitating factors; ‘volume load during operation’, ‘ventilator time in the ICU’ and ‘plasma sodium concentration in the ICU’ contributed to POD. The predisposing and precipitating variables were merged in a final multivariable model, with the results shown in Table 5. Among these, the ‘volume load during operation’ had the strongest predictive influence on POD.
Among CPB variables analysed in Study II, the ‘duration of CPB’, CPB specific ‘fluid balance’, ‘relative arterial pump flow’ and ‘duration of mixed venous oxygen saturation (S\textsubscript{v}O\textsubscript{2} below 75%’ were identified as being univariately associated with POD. The multivariable results are shown in Table 6. In this model, the ‘duration of S\textsubscript{v}O\textsubscript{2} below 75%’ during CPB had the strongest predictive influence on POD.

### Table 5. Multivariable Logistic Regression Analysis with predisposing and precipitating factors

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>Wald</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.10</td>
<td>4.39</td>
<td>1.01 - 1.21</td>
<td>0.036</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.49</td>
<td>4.58</td>
<td>1.11 - 10.99</td>
<td>0.032</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>4.00</td>
<td>3.83</td>
<td>1.00 - 16.06</td>
<td>0.050</td>
</tr>
<tr>
<td>Volume load during operation (L)</td>
<td>2.77</td>
<td>10.71</td>
<td>1.51 - 5.11</td>
<td>0.001</td>
</tr>
<tr>
<td>Ventilator time in ICU (h)</td>
<td>1.20</td>
<td>4.14</td>
<td>1.01 - 1.42</td>
<td>0.042</td>
</tr>
<tr>
<td>Highest temperature recorded in ICU (°C)</td>
<td>2.23</td>
<td>4.06</td>
<td>1.02 - 4.85</td>
<td>0.044</td>
</tr>
<tr>
<td>Sodium concentration in ICU (mmol/L)</td>
<td>1.19</td>
<td>4.30</td>
<td>1.01 - 1.41</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, Intensive Care Unit; OR, Odds Ratio; Cl, Confidence Interval ± 95%

### Table 6. Multivariable Logistic Regression Analysis with variables associated with Cardiopulmonary Bypass

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>Wald</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>1.09</td>
<td>4.34</td>
<td>1.01 - 1.19</td>
<td>0.037</td>
</tr>
<tr>
<td>S\textsubscript{v}O\textsubscript{2} &lt;75% (min)</td>
<td>1.03</td>
<td>10.39</td>
<td>1.01 - 1.05</td>
<td>0.001</td>
</tr>
<tr>
<td>Fluid Balance (mL)</td>
<td>1.00</td>
<td>4.29</td>
<td>1.00 - 1.00</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Abbreviations: S\textsubscript{v}O\textsubscript{2} <75%, duration of venous oxygen saturation below 75%; Fluid Balance, administered volume of crystalloids during CPB, urine excluded; OR, Odds Ratio; CI, Confidence Interval ± 95%

In Study I both predisposing and precipitation variables significantly predicted POD. Of these the precipitating variables gave a slightly better explanatory power than the one based on predisposing factors. The strength increases when predisposing and precipitating factors were combined in the model, being associated with a Nagelkerke $R^2$ value of 0.346, and an area-under-curve (AUC) of 0.802 (P<0.001). In Study II, the tested CPB-related variables were associated with a Nagelkerke $R^2$ of 0.191 and an AUC of 0.707 (P<0.001).
**Merging of the result from Study I and Study II**

Variables from Study I and Study II were merged for multivariable analysis, which was conducted in two steps. Initially the precipitating variables from Study I were merged with the CPB-specific variables form Study II. Variables independently associated with POD are shown in Table 7. The duration of $\text{S}_\text{VO}_2 <75\%$ during CPB from Study II remained among these variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>Wald</th>
<th>95% Cl</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume load during operation (L)</td>
<td>1.86</td>
<td>4.96</td>
<td>1.08 - 3.21</td>
<td>0.026</td>
</tr>
<tr>
<td>$\text{S}_\text{VO}_2 &lt;75%$ (min)</td>
<td>1.02</td>
<td>4.53</td>
<td>1.00 - 1.04</td>
<td>0.033</td>
</tr>
<tr>
<td>Ventilator time in ICU (h)</td>
<td>1.21</td>
<td>4.96</td>
<td>1.02 - 1.43</td>
<td>0.026</td>
</tr>
<tr>
<td>Sodium concentration in ICU (mmol/L)</td>
<td>1.17</td>
<td>4.08</td>
<td>1.01 - 1.37</td>
<td>0.043</td>
</tr>
</tbody>
</table>

*Table 7. Logistic Regression Analysis with precipitating variables from Study I and CPB specific variables from Study II*

Abbreviations: ICU, Intensive Care Unit; $\text{S}_\text{VO}_2 <75\%$, duration of venous oxygen saturation below 75%; OR, Odds Ratio; Cl, Confidence Interval ± 95%

In the second and final step, the predisposing variables from Study I were added to the analysis. The duration of $\text{S}_\text{VO}_2 <75\%$ from Study II remained independently associated with POD also at this step, as did most of the variables presented in Study I. The results are shown in Table 8. However, the variable ‘blood loss during operation’ appeared in the list of independent factors. This variable had previously been rejected in the stepwise backward regression process, both in Study I and in Study II. Diabetes that was identified in Study I was now rejected in the merged process. The logistic regression model appeared robust as most variables remained unchanged in the merged analysis. Again, the variable ‘volume load during operation’ had the strongest influence on POD after cardiac surgery.
The first step of the merged model with precipitating variables was associated with a Nagelkerke $R^2$ value of 0.259, and an AUC of 0.756 ($p<0.001$). The predictive strength increases when the predisposing factors from Study I were added to the regression model, associated with a Nagelkerke $R^2$ value of 0.392, and an AUC of 0.817 ($p<0.001$). This is to be compared with the Nagelkerke $R^2$ of 0.346 in Study I, suggesting an improved predictive strength after the added information from Study II (Table 9). The Receiver Operating Characteristic (ROC) curves for the merged model are shown in Figure 3.

### Table 8. Logistic Regression Analysis of variables from Studies I and II

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>Wald</th>
<th>95% Cl</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.15</td>
<td>7.80</td>
<td>1.04 - 1.26</td>
<td>0.005</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>5.08</td>
<td>4.54</td>
<td>1.14 - 22.63</td>
<td>0.033</td>
</tr>
<tr>
<td>Blood loss during operation (L)</td>
<td>0.16</td>
<td>4.89</td>
<td>0.03 - 0.81</td>
<td>0.027</td>
</tr>
<tr>
<td>Volume load during operation (L)</td>
<td>3.31</td>
<td>9.79</td>
<td>1.57 - 7.02</td>
<td>0.002</td>
</tr>
<tr>
<td>$S_0_2 &lt;75%$ (min)</td>
<td>1.03</td>
<td>5.86</td>
<td>1.01 - 1.05</td>
<td>0.015</td>
</tr>
<tr>
<td>Ventilator time in ICU (h)</td>
<td>1.26</td>
<td>5.29</td>
<td>1.04 - 1.54</td>
<td>0.021</td>
</tr>
<tr>
<td>Highest temperature recorded in ICU (°C)</td>
<td>2.50</td>
<td>4.61</td>
<td>1.08 - 5.79</td>
<td>0.032</td>
</tr>
<tr>
<td>Sodium concentration in ICU (mmol/L)</td>
<td>1.20</td>
<td>4.39</td>
<td>1.01 - 1.42</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, Intensive Care Unit; $S_0_2 <75\%$, duration of venous oxygen saturation below 75%; OR, Odds Ratio; CI, Confidence Interval ± 95%

### Table 9. Logistic models applied on Study I and on the merged analyses of Studies I and II

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Merged Studies I and II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Precipitating only</td>
<td>Precipitating and Predisposing</td>
</tr>
<tr>
<td>Nagelkerke $R^2$</td>
<td>0.214</td>
<td>0.346</td>
</tr>
<tr>
<td>ROC area under curve</td>
<td>0.729</td>
<td>0.802</td>
</tr>
</tbody>
</table>
Detection and documentation of delirium

The aims of Studies III and IV were to validate and compare different methods to detect and document POD in clinical practice, both analysing cohort-A. In Study III, the CAM scale was validated against the reference method. Of the 78 patients diagnosed with POD by the reference method the CAM identified 53, as true positive observations. Additionally, the CAM wrongly depicted 6 patients as having POD, as false positive observations. This gave the CAM a sensitivity of 68% and specificity of 90% (Study III). In Study IV, the clinical database identified 22 out of the 78 patients with POD, which gave a sensitivity of 28%. The comparison made between the clinical database, Nu-DESC and discharge summaries showed that Nu-DESC resulted in an increased detection ability of POD-related symptoms in clinical practice after cardiac surgery.

By the reference method, POD can be divided into subtypes of psychomotor activity and psychiatric symptom profiles. In terms of psychomotor activity, hypoactive delirium was more common than the hyperactive form, both on day 1 and day 4 postoperatively. Of the psychiatric symptom profiles, emotional
symptoms were most common on day 1, while mixed emotional and psychotic symptoms increased on day 4. The ability of the CAM scale to detect delirium in these subgroups was tested in Study III. The CAM appeared to more accurately detect patients with hyperactive signs than those with hypoactive signs. Regarding the psychiatric symptom profile group, the CAM had a high sensitivity in detecting emotional symptoms on day 1, and on day 4 those with mixed emotional and psychotic symptoms (Study III). In Study IV, patients identified as delirious by the clinical database were mainly those expressing hyperactive and mixed emotional and psychotic forms of delirium, respectively. Both the Nu-DESC and the documentation in discharge summaries failed to detect all patients in the different subgroups, but performed somewhat better than the clinical database (Study IV).

The review of discharge summaries in Study IV showed that key words and expressions, such as “confused”, “aggressive and restless” or “disoriented”, associated with inappropriate behaviour appeared more frequently than the other items. In a comparison of documentation within the five POD-related items no significant differences was revealed between how nurses and physicians presented the symptoms. Of interest however, in 23 of the 78 patients diagnosed with POD, discharge summaries wrongly described these patients as being lucid during the hospital stay.

**Economic Consequences of POD**

The overall postoperative cost associated with hospitalisation in the ICU and on the ward, and considering all-type surgery, was 8,200 €. The hospitalisation cost increased for patients with Nu-DESC ≥2 compared to those with Nu-DESC <2. Calculated on median values, the surplus cost was 3,600 €, corresponding to a 45% increase. This difference was associated with the time spent in the ICU whereas there were only small cost differences on the ward. This pattern was observed regardless of the type of surgical procedure. The increased cost associated with the ICU was observed for Nu-DESC scores of ≥3. Older patients were overrepresented among those with Nu-DESC ≥2. However, older patients (≥70 years of age) with Nu-DESC ≥2 did not have higher costs for hospitalisation in the ICU or ward compared with the younger group of patients. A similar pattern was observed for females being overrepresented among those with Nu-DESC ≥2, but had no higher hospitalisation costs in the ICU or ward compared with the males (Study V).
Discussion

The main findings of this thesis showed that POD is common after cardiac surgery, with an incidence of about 55%, as demonstrated for cohort-A and using elaborate diagnostic methods. It was further found that POD was independently associated with both predisposing and precipitating risk factors (Study I). Among precipitating variables, details specific to CPB were also identified and contributing to POD (Studies I-II). Hypoactive delirium was the most common form of symptom profiles, with relevance for the ability to detect POD. The CAM method was validated, but showed a low sensitivity in detecting hypoactive delirium (Study III). Similarly, patients with hypoactive symptoms were often unrecognised in the clinical database. The nurse assessment of delirium symptoms by the Nu-DESC screening did not detect all patients with POD, but identified delirium more effectively than recordings in the clinical database and in discharge summaries (Study IV). Finally, this thesis showed that delirium symptoms recorded by Nu-DESC screening were associated with an increased postoperative hospitalisation cost after cardiac surgery, specifically for the Length of Stay in in the Intensive Care Unit (ICU-LOS). Also, among patients identified with a Nu-DESC score ≥2, the ward requirement costs were the same, regardless of age, gender or surgical procedures (Study V).

POD incidence and symptom profiles

The incidence of POD observed within cohort-A falls in the upper segment of incidence rates reported elsewhere for cardiac surgery, varying between 3% and 73%.

Of importance, cohort-A deliberately enrolled older patients (≥70 years of age) known to have an increased susceptibility of developing POD, which must be considered when comparing results. The selection of patients most likely contributed to the high POD incidence reported here. In a previous study, sharing the same surgical settings and POD assessment methods, 12 of 52 patients (23%) were identified with POD. This study did not have a restricted inclusion to older patients, with a mean age of 70 years and nearly 7 years younger than in cohort-A. Also, that study included only CABG patients, which might have lowered the POD incidence further. This assumption finds support in Study I, showing that the complexity of the surgical procedures influenced the POD occurrence, at a univariate level. Temporal details must also be considered in the comparison of these two studies, separating them by almost 10 years. On one hand, surgery, CPB, anaesthesia and warding methods might have improved, but on the other hand the selection of patients being referred to surgery may have changed to those with more comorbidity.
Within cohort-A, POD was subdivided into psychomotoric activity and in psychiatric symptom profiles. The majority of POD patients had hypoactive delirium, a finding that supports previous observations.\textsuperscript{34,48,97,98} Mixed psychotic and emotional was the most common among those with psychiatric symptom profiles. Few studies have investigated the appearance of psychiatric symptom profiles of delirium, and less so after cardiac surgery. These, in particular the psychotic symptoms, are less frequently observed than those of psychomotor activity, but are diagnostically useful when they appear. It is most likely a sign of delirium when a patient without a previous history of psychotic diseases unexpectedly expresses such symptoms.\textsuperscript{99}

In cohort-B, symptoms of delirium were assessed by Nu-DESC screening in the postoperative care after cardiac surgery. The cohort included all age groups and all types of surgery including CPB. The occurrence of a Nu-DESC score ≥2 was 20%. This figure can be compared with that of a previous study sharing the same surgical setting and with an open inclusion of age groups, reporting a POD incidence of 23%.\textsuperscript{34} By backward counting from cohort-B, and with a demonstrated overall sensitivity of 85% for the Nu-DESC screening,\textsuperscript{49} the incidence of POD after cardiac surgery becomes in the range of 24%. However, the former study\textsuperscript{34} had a restricted inclusion of patients undergoing CABG surgery only, and therefore a higher incidence rate of 23% would have been anticipated for an all-type surgery inclusion.

**POD risk factors after cardiac surgery**

A variety of risk factors have been proposed to cause POD after cardiac surgery.\textsuperscript{38,100} The present thesis confirms many of these findings, but also suggests new variables not previously identified. Risk factors were here subdivided into predisposing and precipitating variables. The predisposing factors address risks known in advance of surgery. These allow for risk evaluation that might affect the decision to operate or not. For susceptible individuals safety measures can be taken to protect against POD. The precipitating factors reflect intraoperative and early postoperative events, and if known, might be controlled to avoid POD. The subdivision was also conducted for statistical considerations to condense the number of variables tested in the final model of logistic regression. The procedure also allowed for improved co-variability testing within each group of variables. Therefore in Study I, precipitating and predisposing factors were first separately analysed and then combined.

CPB hides numerous potential risk factors for POD. Only CPB time was evaluated in Study I, whereas a more detailed analysis of CPB was conducted in Study II. Study II shared the relevant predisposing variables with Study I. For this thesis;
variables from both these studies, I and II, were merged into a new multivariable analysis. This analysis was made with the intention of investigating whether these variables together would affect the overall outcome. This new analysis revealed that the main results from both studies remained largely intact with only minor changes. For example, the variable ‘diabetes’ became rejected and the variable ‘blood loss during surgery’ became included in the merged model. The merged analysis also showed an improved predictive strength of the logistic model after the additional information from Study II.

**Predisposing risk factors**

This thesis confirmed that advanced age adds a profound risk of developing POD. The predictive impact of age on POD is probably underestimated here, as only patients ≥70 years of age were included in cohort-A, which restricts the variability of this variable. Advanced age is a well-known risk factor and has been reported in several studies, including for cardiac surgery patients.\textsuperscript{101-104} According to Bryczkowski et al. (2014) the risk of developing delirium increased by approximately 10% per year increment, demonstrated for trauma patients ≥50 years of age admitted to surgical intensive care.\textsuperscript{105} The multivariable logistic output of Study I showed a similar risk increase of 10 % per year.

Advanced age might reflect a variety of contributing mechanisms to the development of POD. An example is how the cholinergic reserve decreases with age,\textsuperscript{106} possibly contributing to a susceptibility to drugs with anticholinergic side effects, such as Furosemide.\textsuperscript{107} Loop diuretics are commonly used in ICU care, and thus potentially contribute to POD. Unfortunately, in this thesis administered drugs were not incorporated into the analyses of risk factors. Age is also associated with atherosclerosis, which increases the risk of cerebral embolization, especially during aortic manipulation.\textsuperscript{74,108-110}

Diabetes is another well-known risk factor for atherosclerotic disease.\textsuperscript{111} Moreover, the atherosclerotic disease might lead to impaired cerebral blood flow which is not an unusual finding in patients with diabetes.\textsuperscript{112} An impaired cerebral blood flow may be difficult to control during CPB and worsen the cerebral haemodynamics and could possibly lead to neurological complications such as POD.\textsuperscript{113} The results of Study I showed that diabetes increased the risk for POD by 3.5 times and has been reported as a risk factor for delirium in several other studies.\textsuperscript{28,100,114} However, in the merged analysis combining Studies I and II, diabetes was rejected as an independent risk factors of POD.

Also, gastric ulcer was associated with POD, but only having a borderline significance in Study I. Most likely, this variable is false positive and represents a
statistical type I error. A hypothetical interpretation of this finding may imply that preoperative gastric ulcer is a general stressor, by which it increases the risk for POD.\textsuperscript{115}

**Precipitating intraoperative risk factors**

Of special interest among the identified precipitating risk factors was the variable ‘volume load during operation’. This variable had the strongest predictive influence on POD in Study I and also in the merged analysis combining Studies I and II. In Study II, the ‘CPB fluid balance’ was analysed rather than the overall intraoperative balance. The variability of CPB fluids is much lower as it includes a standardised priming volume. Even so with this restriction, the ‘CPB fluid balance’ showed to be an independent risk factor associated with POD. To our knowledge the association between intraoperative volume load and POD has not been previously reported in cardiac surgery. However, Olin et al. (2005) found that both intraoperative and accumulated 24-hour crystalloid infusion were risk factors for POD among patients undergoing major abdominal surgery.\textsuperscript{116} These findings are in line with our results, as the variable ‘volume load during operation’ was the accumulated crystalloids administered on the anaesthetic side and from the perfusionist during CPB. The variable excluded blood products given, urine output and blood loss.

The causal mechanisms for how a volume load contributes to POD after cardiac surgery is unknown and there are various reasons why fluid is given during surgery. It can be speculated that the relative volume overload, or volume requirement, reflects a capillary leakage secondary to a systemic inflammatory response syndrome, known as ‘SIRS’. It is generally believed that the contact between the artificial surfaces of the CPB-circuit and blood components contribute to an inflammatory process.\textsuperscript{117} There is also evidence to suggest that a systemic inflammation contributes to the development of delirium.\textsuperscript{118} Unfortunately, the inflammatory effect of CPB in relation to POD was not investigated in this thesis. Another factor for volume requirement during surgery is to control hypotension and hypovolemia. Hypotension might cause inadequate cerebral blood flow leading to POD.\textsuperscript{119,120} This hypothesis was not supported by Wesselink et al. (2015), who did not find an association between intraoperative hypotension during cardiac surgery and POD. However, they rather concluded that the duration of hypotensive episodes seemed to be associated with POD.\textsuperscript{121}

Intraoperative blood loss is an additional reason for an increased volume requirement during surgery. Blood loss is a known contributor to POD after vascular surgery,\textsuperscript{122} spinal surgery\textsuperscript{123} and after major abdominal surgery.\textsuperscript{116} This variable was included in the risk factor analysis of Study I, but became excluded
in the stepwise regression process, and thus not independently associated with POD. However, in the merged analysis, combining Studies I and II, ‘blood loss’ remained during the regression process and was found independent, but negatively associated with POD together with the variable ‘volume load during operation’. Of interest, at univariate level the blood loss was modestly, but non-significantly higher in patients with POD. At multivariable level, an increased blood loss protected against POD suggesting a complex interaction with other variables. It may be presumed the ‘blood loss’ mainly interacted with ‘volume load during operation’ and the ‘duration of S\textsubscript{O}\textsubscript{2} <75%’ added from Study II, although these assumptions were not further explored.

Intraoperative blood loss intuitively contributes to a decrease in haemoglobin levels, unless compensated by transfused blood. Reduced levels of haemoglobin could not be confirmed in our analysis, either intraoperatively or postoperatively. Otherwise, a low concentration of haemoglobin limits the oxygen carrying capacity,\textsuperscript{124} which might contribute to POD, as previously demonstrated after cardiac surgery.\textsuperscript{125,126} An insult to the brain caused by hypoxaemia is known to cause delirium.\textsuperscript{127} Also, cerebral desaturation during CPB is known to be associated with a negative neurological outcome,\textsuperscript{128} but whether desaturation during CPB causes POD is unknown. In Study II the duration of S\textsubscript{O}\textsubscript{2} <75% was the strongest independent predictor of POD among the CPB specific risk factors. Our results were recently confirmed by Leenders et al. in 2018.\textsuperscript{129} The oxygen supply to the brain during CPB is mainly determined by the pump flow and haematocrit levels and these variables might therefore be potential risk factors behind POD. In contrast to these findings, Lopez et al. (2016) reported that intervals of hyperoxic cerebral reperfusion during CPB contributed to POD.\textsuperscript{130} An interpretation would suggest that constantly keeping the S\textsubscript{O}\textsubscript{2} very close to the 75% target during CPB is a preferable strategy to avoid future POD.

**Precipitating postoperative risk factors**

We found that patients with POD were characterised by a significantly longer ICU ventilator time than patients without POD. The ventilator time was approximately 3 hours longer in the POD group of patients. In the multivariable analysis, combining Studies I and II, the risk of developing POD increased by 26\% per additional hour of ventilation. The time of postoperative ventilation might depend on many factors;\textsuperscript{131-133} such as comorbidities,\textsuperscript{134} drugs given to the patient,\textsuperscript{131} clinical guidelines,\textsuperscript{132} and the nurses’ experience of extubating patients.\textsuperscript{133} Extubation may also vary because of anaesthetic routines.\textsuperscript{135} There is evidence to suggest that a prolonged ventilator time increases the risk of developing POD\textsuperscript{71,136} and that an intubation period extending beyond 24 hours is strongly related to the development of POD.\textsuperscript{137} In contrast and conversely,
Stransky et al. (2011) proposed that POD after cardiac surgery leads to a prolonged requirement of ventilation.  

In Study I, as well as in the analysis combining Studies I and II, the highest body temperature recorded in the ICU was associated with POD. At this early stage, an increased body temperature is not an indicator of a postoperative infection. Rather, a postoperative fever is caused by the inflammation following surgery and the metabolic response to tissue trauma, blood transfusion, and blood accumulation in confined spaces, but also the presence of drainage and medications used during the perioperative period. In addition, after cardiac surgery postoperative fever might also reflect CPB factors, wound-blood recycling and hypothermic rebound.  

In Study I, as well as in the analysis combining Studies I and II, a modest but significant increase in plasma sodium concentration was recorded in the early postoperative period, found to predict POD. Sodium was an independent risk factor, and thus not relying on the variable ‘volume load during operation’. The statistical analysis could not verify a correlation between these two variables, suggesting that the electrolyte disturbance was not the result of intraoperative volumes given. An association between sodium concentration and POD in cardiac surgery patients has previously been reported. However, the exact mechanism by which the disturbance in sodium concentration contributes to POD remains unclear.  

From 1964 until 2014, 196 studies have been published, proposing 123 different risk factors for POD in patients undergoing cardiac surgery. However, for each factor identified, the risk of developing POD increases beyond reasonable limits. It is likely that a person with multiple risk factors is at greater risk of developing POD than a person with few factors. Nevertheless, interaction mechanisms are to be presumed between all these variables and many of them would probably become rejected in a merged logistic regression, as demonstrated here when combining the variables of Studies I and II. The logistic models in this thesis confirm that both predisposing and precipitation factors contribute to POD. Some of these factors are possible to compensate for in the clinical care situation; for example the volume of crystalloid infusions given during the operation and keeping the $S_{O_2}$ close to the baseline during CPB. Others factors may serve as predictive instruments when assessing risks associated with a planned cardiac procedure and POD development in particular.
Detection and documentation of delirium

The reported incidence of POD varies substantially in different studies. These differences might reflect how delirium was assessed and diagnosed. Studies based on assessment scales in the hands of experienced researchers often report a higher incidence of delirium. In a recently published review by van Velthuijsen et al. (2016), 28 different instruments for detecting delirium were identified, and it was recommended that most of these instruments require knowledge and training to handle. They concluded that two of these 28 instruments were the most suitable for daily clinical practice, the Nu-DESC and the CAM. The Nu-DESC, being quick and easy-to-use, was proposed to be the most functional method in daily care by nurses. The CAM, on the other hand, has been reported to offer a high sensitivity and specificity, and was suggested to be the best diagnostic instrument for delirium in the hands of nurses. Both these scales have been evaluated in this thesis.

Screening scales for delirium

Of the two screening scales used here, the CAM scale is the most well-known and used, in both clinical practice and for research. The CAM has been translated into several languages and adapted to various care settings. Changes to the CAM protocol have also been made to allow rating of delirium severity and to detect subtypes of delirium. Here in Study III, the original CAM was used, as the intention was to follow the patients throughout their hospital stay rather than for a specific ward level. Our results showed that the CAM had a relatively low rate of false-positive observations and therefore was associated with a high specificity of 90%. On the other hand, the sensitivity was less precise, 68%, due to a relatively large proportion of false-negative observations. The results of Study III suggest a somewhat lower accuracy of the CAM than being reported in other validations and care settings. It has been shown that the CAM requires knowledge and training. In a study by Rolfson et al. (1999) the CAM had an overall sensitivity of 70% and a specificity of 100%, but the results varied between nurses and physicians. In the hands of nurses, the sensitivity was as low as 13%. A similar problem with a low CAM sensitivity in the hands of nurses was reported by Lemiengre et al. (2006). They found that nurses had difficulties in identifying an acute onset, fluctuation, and altered level of consciousness when using the CAM among geriatric patients.

Also the Nu-DESC instrument, with its intended easy-to-use screening, has been found to be problematic in detecting delirium. In a study by Hargrave et al. (2017), with a Nu-DESC cut-off score of ≥2 and with no additional cognitive testing, it was reported to have a sensitivity of 42% and a specificity of 98% when
used among patients in different care settings. The sensitivity increased by adding an attention test. In our research the Nu-DESC was used by nurses without any additional cognitive testing. The results in Study IV showed that the Nu-DESC performed better in identifying patients with POD than the documentation provided by both nurses and physicians in their discharge summaries. Another comparison was against the clinical database, and how POD was registered at discharge. In fact, the clinical database offered the lowest recognition of POD of all tested methods; CAM, Nu-DESC and discharge summaries, by identifying only 22 out of the 78 patients with POD. Of importance though, the clinical database is not an instrument for systematic assessment such as the Nu-DESC and the CAM. Another reason behind the lack of precision of the clinical database was how POD was defined, in terms of a ‘yes or no’ question about confusion which was mainly based on the nurse’s clinical impression of how the condition affected the patient’s warding. According to van Eijk et al. standardized assessment methods are strongly recommended because of the low sensitivity associated with a ‘clinical impression’. Moreover, a single observation or instrumental assessment is insufficient and a poor strategy to identify these patients because of the fluctuating course of delirium.

A challenge with delirium assessment methods is to identify those patients with more subtle forms of symptoms, in both psychomotoric activity and in psychiatric symptom profiles. It is obvious that patients with extrovert characteristics, as with hyperactive delirium, are more easily recognized than those with introvert symptoms. This is supported here, as the patients with hyperactive delirium more often occurred among those recorded in the clinical database and in discharge summaries. In our studies, the majority of POD patients had hypoactive delirium, which confirms previous observations. Unless carefully investigate by, also including a cognitive assessment, these patients are at risk of not being recognized in the clinical care. The lack of cognitive assessment is proposed here to explain the shortcomings of both the CAM and the Nu-DESC. As for psychiatric symptoms profiles, mixed psychotic and emotional symptoms seem to be easier to detect. The results of Study III showed that the CAM almost detected all patients with mixed psychotic and emotional symptoms. A similar pattern was observed in Study IV for both Nu-DESC screening and how these patients were registered in the clinical database.

**Documentation of delirium**

A limited knowledge about delirium and lack of screening scales are barriers to recognising delirium. This was confirmed in study IV, showing that many patients with POD were not recognised or diagnosed by neither the nurses nor the physicians in the discharge summaries. However, there were no differences
between how nurses and physicians failed to document POD. This is in contrast to the results reported by Bellelli et al. (2014). Of the 322 physicians participating in the study 85% correctly identified delirium in the patient records whereas the corresponding figure for the 225 nurses was 50%. In comparison, in Study IV nurses correctly described POD in 53% of their 59 discharge summaries, which is in line with the results presented by Bellelli et al. (2014). Moreover, nurses identified 72% of the 78 patients with POD by using the Nu-DESC. These figures are based on the same patient cohort-A. However, although the Nu-DESC had been introduced at the Cardiotoracic Surgery Unit for research purposes, neither the nurses nor the physicians had been informed about using the Nu-DESC as a diagnostic reference of POD. It has been reported that the awareness of both nurses and physicians in recognising delirium improves when assessment scales are introduced. In contrast to this statement, Guenther et al. (2012) showed that delirium was more correctly described in the patient records when based on subjective clinical impressions rather than objective observations with the Confusion Assessment Method for Intensive Care Unit (CAM-ICU). This was analysed in an ICU setting of general and cardiac surgery. Despite these findings, there were delirious patients according to CAM-ICU discharged to the warding unit without being recognised with subjective clinical impressions.

The lack of information about POD in discharge summaries may also reflect the health professionals’ difficulties in identifying hypoactive delirium. Delirium was documented by both nurses and physicians with only a few words describing symptoms associated with inadequate behaviour, such as “confused”, “aggressive and restless” or “disoriented”. The documentation of POD symptoms did not differ between nurses or physicians. There was also a group of POD patients who were incorrectly described as lucid by both nurses and physicians. Nurses appeared more likely to incorrectly document the patients as lucid compared with the physicians. Of particular interest, neither the nurses nor the physicians described ideas about the mechanism behind POD and how this may have been treated.

It has been suggested that physicians more often document details about the diagnosis of delirium while nurses often mention signs or symptoms. It has been proposed that nurses usually describe delirium in the context of the patient’s mental status and behaviour in terms of dementia. The documentation and recognition of delirium was found to improve when an ongoing educational programme was introduced, including lectures and group discussions among both nurses and physicians. On the other hand, Akechi et al. (2010) showed that a short education offered to nurses improved their care for patients with delirium, but no improvement was seen in the nurses’ ability to explain delirium symptoms in the patient records. They concluded that the nurses’ lack of ability to explain delirium was due to little focus on delirium during nurse training.
The failure to detect delirium is a missed opportunity to help an individual patient, which can lead to a negative outcome and consequences for the patient and to increased healthcare costs.

**Economic Consequences of POD**

The results of Study V showed that the patients with Nu-DESC ≥2 required a prolonged postoperative hospitalisation period associated with increased costs. The increase was predominantly due to a prolonged ICU warding. This finding is similar to the results described by Brown et al. (2016) with an increased ICU-LOS in patients with delirium after cardiac surgery and thereby an increase in ICU and hospital costs. Several reasons may be anticipated why patients with POD require ICU care. At a group level, patients with POD are older and have co-morbidities which may require a prolonged ICU stay. Also, POD is associated with an impaired cognition, which affects the patient’s ability to participate in the care and therefore requires a higher care level. POD might also develop as a result of a medical condition requiring prolonged mechanical ventilation. Milbrandt et al. (2004) found that patients in need of mechanical ventilation were more prone to develop delirium, resulting in a prolonged ICU stay with higher costs.

There are studies demonstrating that patients with severe delirium often require ICU warding. Study V showed that costs increased when the Nu-DESC score reached a level of three and higher. It must be emphasised that the Nu-DESC does not allow grading of delirium severity as it only assesses symptoms of delirium. The reason behind our findings may be that patients with Nu-DESC scores of less than three are manageable on the ward, associated with lower costs, while patients with higher scores require a higher level of care and are moved to the ICU.

The results in Study V were differentiated for age, gender and separated for the type of surgical procedure. These are all known risk factors for POD. However, in the comparison between groups, Nu-DESC ≥2 and Nu-DESC <2, patients with delirium symptoms consumed longer warding and therefore increased costs. However, for those patients recorded with Nu-DESC ≥2 no difference in hospitalisation costs were identified between age groups or gender. These results suggest that patients with delirium symptoms recorded with Nu-DESC receive the same LOS.

Intervention studies, in care settings other than cardiac surgery, have shown that costs associated with delirium can be reduced. The most well-known of these intervention studies is the Hospital Elder Life Program (HELP) for prevention of
delirium. This is a multicomponent intervention targeting cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration.\textsuperscript{29} This programme has been reported to reduce the hospital costs by approximately $831 per patient intervention.\textsuperscript{158} The model has also been found to save $9,446 per participant in yearly nursing home costs.\textsuperscript{159} Also, Rudolph and colleagues (2014) demonstrated how it was possible to reduce the LOS for patients admitted to a medical ward by introducing a ‘Delirium Toolbox’. This is a simple intervention protocol which was designed for cognitive stimulation and sleep promotion. The reduction in LOS for patients with delirium resulted in a decrease in direct costs with $1390.\textsuperscript{157} Implementation of different interventions might involve additional resources appearing more costly at the beginning than the care provided at present. However, the return on these investments might improve the patient’s outcome, shortening the LOS and thereby reducing hospitalisation costs.

**Ethical considerations**

There are some ethical considerations to take into account when studying older patients under various vulnerable conditions. In cohort-A, patients were asked for consent to participate in the study, both in writing and orally at admission to the Cardiothoracic Surgery Unit prior to surgery. For many of these patients, this is a moment when they may feel vulnerable and potentially pressured to participate in the study. However, the oral and written information addressed these issues of vulnerability and that the patient could discontinue participation at any point. If they had concerns about their participation, the patient was also offered the possibility of contacting the study nurse, during their hospital stay and also after discharge.

The interviewing associated with the assessments scales was extensive and might have been exhaustive for the patient, especially in the postoperative day one. At this time point the patient was offered to delay the interview to the next day, being within the temporal tolerance of the research protocol. The questions asked of the patient were read out loudly. If the patient had a hearing impairment they were allowed to read the questions asked. Giving support to complete a questionnaire is valuable when obtaining data from older people.\textsuperscript{160} Some of the assessment questions may have been intrusive or difficult to answer. The intention during the interview was to be sensitive to the patient's needs, particularly if they felt uncomfortable with the situation. Patients were also offered the opportunity to be interviewed in a separate room, if preferred. If the patient showed an inability to continue, the interview was ended. These circumstances explained some of the exclusions.
Patients for cohort-B were enrolled from the clinical database. Research involving registries primarily concerns the personal privacy and data security. Although the ethical jurisdiction allows data retrieval without requesting consent, the Personal Data Act requires all research patients to be fully informed. Upon enrolment at the Cardiothoracic Surgery Unit at Heart Centre, Umeå University Hospital, patients are informed about and asked for approval to register data in various databases used for clinical practice and also for research purposes. In order to preserve the personal integrity in cohort-B, data were de-identified and encoded in protocols designed for the purpose of the study. These data were stored in a safe place and were not distributed outside the research group.

**Methodological considerations**

The studies included in this thesis have limitations that must be considered.

**Study samples**

In cohort-A, the inclusion of patients ≥70 years of age was based on a previous study within the research group, to validate the Swedish version of the Nu-DESC scale. With the inclusion of older patients the incident of POD was expected to be higher. However, this selection of older patients only, limits the generalisation of the presented results in Studies I-IV.

In cohort-B, for Study V, the inclusion of patients was limited to those undergoing cardiac surgery with CPB, and to those with recorded data. Database studies do not reach beyond the quality of the documented data. Also, the results in study V cannot be generalised beyond the local setting and on how the Nu-DESC instrument has been locally implemented.

**Delirium diagnosis**

In Studies I-IV, the POD diagnosis was set by two experienced researcher specialised in geriatric medicine. This occurred after patient discharge, based on the assessment with the MMSE and the OBS scale carried out by two study nurses. Establishing a POD diagnosis after having met and interviewed the patient might have improved the diagnostic precision. Some of the patients with POD might also have been overlooked as the assessment with the OBS scale was performed only twice during the patients’ hospitalisation, day one and day four postoperatively. On the other hand, during the interviews with nurses caring for the patient, the OBS scale asked questions about symptoms of delirium occurring in between the two assessment points which might have compensated for this problem. Also, the timing of the assessments is important to consider. Cognitive
function early postoperatively after surgery is likely influenced by postoperative recovery, medications given during and after surgery and other physiological causes exemplified by pain. Another issue with the assessments for POD is the lack of continuity. All assessments were conducted by two of the researchers in the team, but due to of logistics, not all patients were interviewed by the same researcher. This might have reduced the possibility of detecting fluctuations in the patient’s cognition, which among other observations, is a sign of POD.

In Study V, the Nu-DESC scale was used to report the overall incidence of POD symptoms. This incidence might be an underestimation since the Nu-DESC is not a diagnostic instrument and lacks a cognitive assessment. In our previous research of POD after cardiac surgery we have shown that the Nu-DESC instrument fails to recognise some patients, in particular those with hypoactive symptoms.

**Data analyses**

Study I was based on a relatively small study sample in relation to the extensive number of variables extracted for the analysis. However, other POD contributing factors are to be sought among factors beyond these analysed. CPB variables were only briefly addressed in Study I, due in part to the already extensive number of available data analysed. In view of Study II, these CPB variables were considered important as the predictive strength of the model improved when adding information from Study II to Study I. The results from the merged analysis are presented in this thesis. Also, in Study II, due to the observational nature of the study, no definite conclusions can be made regarding different CPB strategies.

Unfortunately, although a large number of variables were analysed in Study I, the pharmacological interactions were not investigated. We were unable to explore these interactions due to an inconsequent documentation of the use of anaesthetics, analgesics and sedative medications on the unit during the study period in 2009. These pharmacological interactions might have influenced the patients’ cognition or even caused POD.

In Study IV, the extraction of expressions and keywords in the discharge summaries of the 78 patients with POD was performed by only one person, which may have resulted in lost details. However, the text describing POD in the discharge summaries was short and easy to grasp. Key words and expressions extracted from the discharge summary were reviewed together in the research group. If any key words or expressions appeared unclear, a new review of the discharge summary was done. Also, in study IV, the clinical database was
compared with systematic screening scales in detecting POD. The clinical database is not an assessment scale as it lacked a clear definition of delirium.

The hospitalisation costs referred to in Study V are only estimates based on the period of hospitalisation in the ICU and on the ward. This was calculated from details extracted in the clinical database and standardised costs obtained from the hospital’s accounting department, rather than truly recorded costs for each patient.

**Screenings scales for delirium**

In Study III, the precision of the POD diagnosis according to CAM may have been negatively influenced by how the scale was used. The CAM is described as an observational instrument that requires minimal interviewing, but repeated assessments are required. Only two interviews with the CAM were conducted postoperatively which might have influenced the detection rate of POD by this scale. Also, the English version of the CAM was used because there was no validated Swedish version at the time of interviewing. Another issue affecting the comparison of the CAM with the reference method might be that the two assessment methods refer to different DSM manuals. The CAM refers to an older diagnostic manual, DSM-III-R, while the POD diagnosis in Studies I-IV is based on DSM-IV-TR criteria. It has been suggested that DSM-IV-TR criteria offer a higher sensitivity for detecting delirium than the DSM-III-R.

In cohort-A, the Nu-DESC was introduced for scientific purposes and was not intended for clinical use, which might have affected the incidence of delirium symptoms reported by the nurses. Prior to the study period in 2009 the nurses on the Cardiothoracic Surgery Unit were offered a one hour training session. About half of the participating nurses attended the training. After this session a two-week run-in period followed for the Nu-DESC assessments which included hands-on training and support from two researchers in the team. A more extensive educational programme with follow-ups might have improved the POD incidence reported with the Nu-DESC in 2009. After the study period in 2009, an educational programme about POD and Nu-DESC assessments has been introduced on the unit, with a presumed beneficial effect within cohort-B and on Study V.
Conclusions

- A variety of both predisposing and precipitating risk factors contribute to delirium after cardiac surgery with CPB. Particular attention is paid to the influence from the intraoperative volume load the patient becomes exposed to (Study I).

- CPB contributes to POD, in particular the negative effects caused by episodes of low mixed venous oxygen saturation (Study II).

- The CAM scale is unable to detect the more subtle forms of hypoactive and psychotic delirium (Study III).

- Important information about POD is insufficiently and inadequately documented in discharge summaries by both nurses and physicians, and in the clinical database, all being important links of communication between caregivers. Symptom screening by the Nu-DESC scale improves the recognition of POD (Study IV).

- Delirium symptoms, assessed by the Nu-DESC scale, are associated with increased hospitalisation costs because of a prolonged ICU ward requirement after cardiac surgery (Study V).
Clinical implications

- Knowledge about predisposing risk factors is beneficial in the referral process to surgery, in order for both the patient and the caregiver to predict the occurrence of POD.

- Knowledge about precipitating risk factors is beneficial as it helps to alter or adapt surgical procedures, CPB strategies and warding methods to avoid POD.

- POD with subtle symptoms is difficult to detect in clinical practice, even with use of the CAM and Nu-DESC instruments. Presumably, this is because these scales lack a cognitive testing.

- A clinical database without a clear definition of delirium fails to identify these patients. It is suggested here that a database should record information obtained by delirium assessment methods.

- POD is associated with negative consequences for both the patient and healthcare. These negative effects, including costs, might be reduced in response to interventions to detect, prevent and treat POD.
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