Novel risk factors for poor outcome in frail cardiac surgery patients

Arends, B.C.

STELLINGEN

behorende bij het proefschrift

Novel risk factors for poor outcome in frail cardiac surgery patients

1. De bevolking veroudert en het aantal ouderen dat hartchirurgie nodig heeft neemt toe, waardoor het identificeren van preoperatieve risicofactoren belangrijker wordt in een poging om ongunstige functionele uitkomsten, zoals verlies van kwaliteit van leven en invaliditeit, te verminderen – dit proefschrift
2. Preoperatief screenen op specifieke kwetsbaarheidskarakteristieken zoals polyfarmacie is een simpel en effectief middel om hoog risico patiënten vroegtijdig te signaleren – dit proefschrift
3. Preoperatieve risicofactoren geassocieerd met postoperatieve chronische pijn en een verminderde kwaliteit van leven zijn; polyfarmacie, alleenwonend, verminderde mobiliteit, verminderde lichamelijke functie en een reeds verminderde kwaliteit van leven voorafgaand aan de operatie – dit proefschrift
4. Kwetsbare oudere patiënten vertonen vaak afwijkingen in ademhalingsfrequentie in de vroege postoperatieve fase na hartchirurgie. Een afwijkende ademhalings-frequentie is een risicofactor voor het optreden van een klinische verslechtering – dit proefschrift
5. Frailty in elderly care shifts focus from organic-specific diagnoses to a holistic perspective, focusing on their increased risk to adverse outcomes due to an impaired ability to maintain homeostasis when faced with stressors. Early identification allows for better monitoring and informed decision-making, potentially reducing the risk of harm from invasive procedures or certain medications – dit proefschrift. Clegg et al. 2013, The Lancet
6. We've been wrong about what our job is in medicine. We think our job is to ensure health and survival. But really it is larger than that. It is to enable well-being. And well-being is about the reasons one wishes to be alive – Atul Gawande
7. The greatest medicine of all is teaching people how not to need it – Hippocrates
8. The preservation of health is easier than the curation of disease – Bartlett Joshua Palmer
9. The greatest glory in living lies not in never falling, but in rising every time we fall; resilience is the key to succes – Nelson Mandela
10. Leer vertrouwen, door angst te durven voelen

Novel risk factors for poor outcome in frail cardiac surgery patients

Britta C. Arends

Novel risk factors for poor outcome in frail cardiac surgery patients

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Novel risk factors for poor outcome in frail cardiac surgery patients

Nieuwe risicofactoren voor slechte uitkomsten in kwetsbare patiënten die hartchirurgie ondergaan

(met een samenvatting in het Nederlands)

Proefschrift

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“To be is to do”

Socrates

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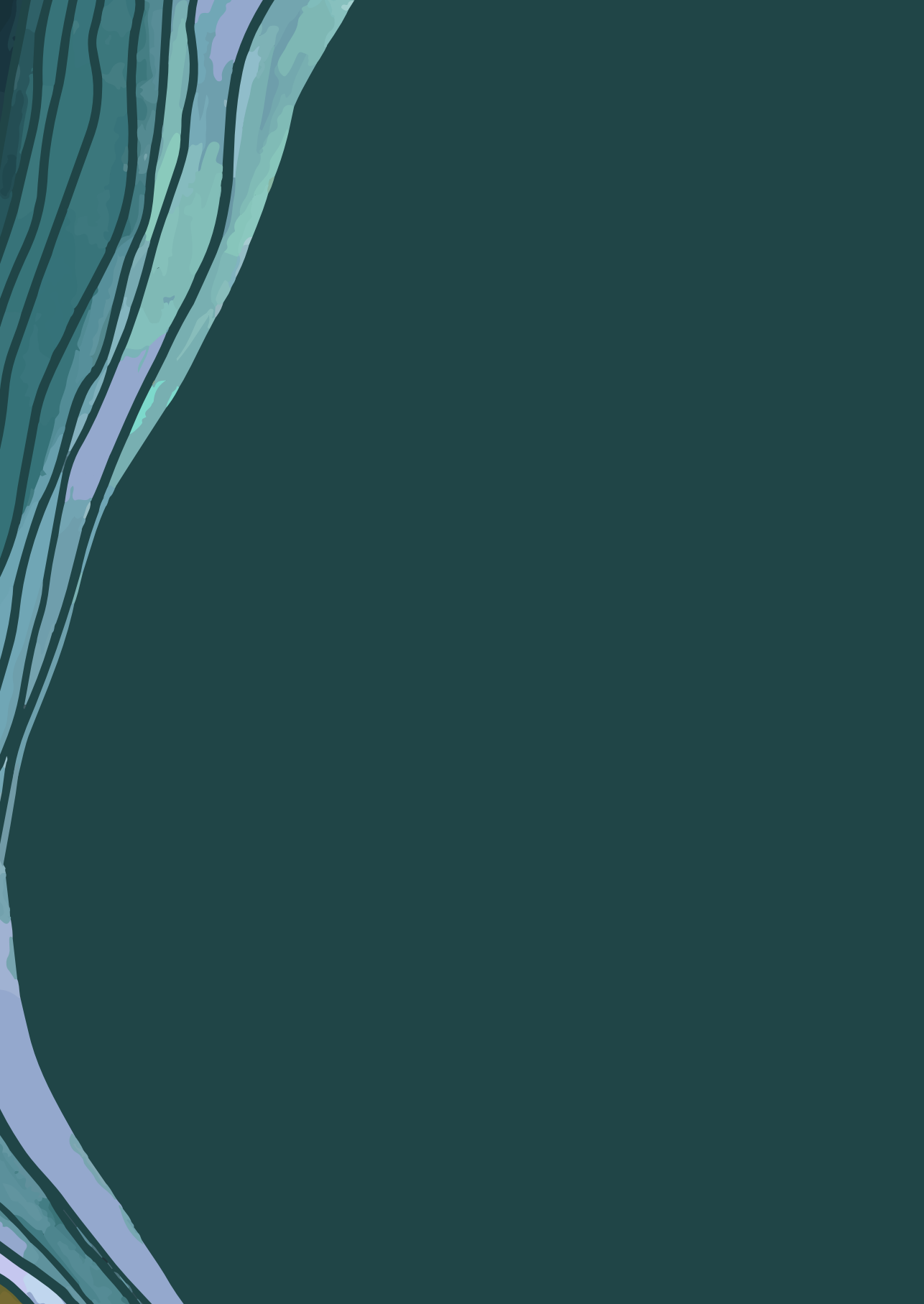


Chapter 1

General introduction

GENERAL INTRODUCTION

Population ageing reflects a human success story of increased longevity due to improved public health, medical innovations and scientific advances.[1] The elderly population grows as mortality rates decrease and people live longer. However, a longer life span has led to new challenges: with advanced age the prevalence of chronic diseases and frailty has increased. In the event of illness, or after major surgery, older patients are at risk for new disabilities and loss of independence. Although surgery in the elderly is relatively safe, maintaining quality of life and self-reliance of surgical patients pose major future challenges for surgeons and anesthesiologists.

Cardiovascular disease and stroke are among the leading causes of death for the population aged 60 years and older.[1] Cardiac surgeries, such as coronary artery bypass grafting and heart valve replacement are part of the most commonly performed surgeries globally in adults.[2] With the ageing population and innovations in healthcare, the elderly represent the fastest growing group of patients referred for cardiac surgery.[3] Elderly patients have consistently shown to derive benefits from cardiac surgery.[4–9] However, perioperative care for older patients is complex, as advanced age is frequently accompanied by a larger burden of comorbid conditions, polypharmacy and frailty.[10–12] A considerable number of elderly experience a postoperative complication and old age is associated with a 2- to 4-fold increased risk of postoperative morbidity and mortality.[10–12]

Major complications after surgery will inevitably lead to loss of independence and disability.[3,10,12] This indicates that identifying elderly patients at a higher risk of adverse outcome may allow for more enhanced perioperative health care. Frailty is an age related state of functional decline, characterized by an accumulation of age- and disease-related deficiencies (**Figure 1**).[13]

Frailty has a multidimensional etiology, which includes deficits related to physical performance, nutritional status, mental health and cognition, and is an emerging risk factor for adverse postoperative outcomes. Frail patients may therefore have limited physiological reserves and low resilience, making them more prone to postoperative complications and poor functional recovery.[3,14,15] Also, frail patients are often exposed to polypharmacy to treat multiple comorbidities. However, the potential harm from multiple medications might outweigh their benefits. Polypharmacy in elderly can result in a burden of treatment including medication interactions, side effects such as increased risk of falls, or errors in medication management, affecting overall health and quality of life. Quality of life is important at all ages, but as we grow older, it becomes crucial for the remaining years ahead.

Figure 1. Frailty, an age related state of functional decline.

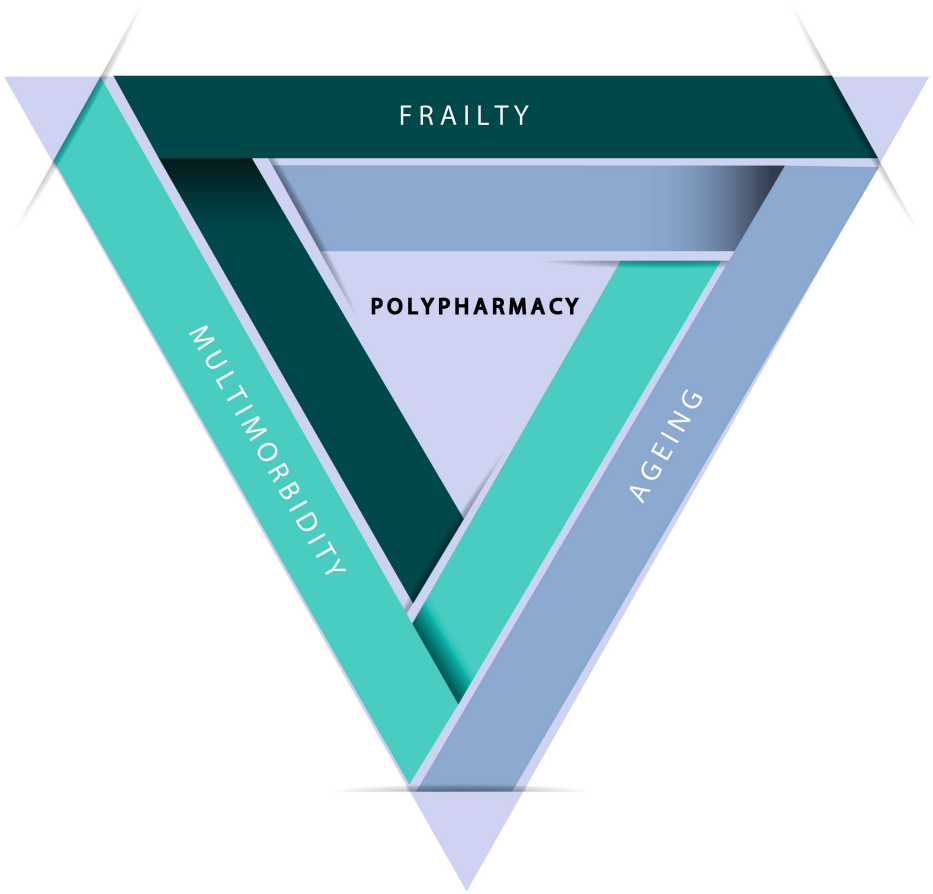
Exploring the implications of polypharmacy in the high risk elderly patient

Identifying preoperative frailty can improve risk stratification in older cardiac surgery patients.[3,16,17] However, many barriers exist to implement preoperative frailty assessments, as these assessments are time-consuming and there is a lack of clarity on which frailty assessment to choose.[10,18,19] A focus on specific frailty domains is more straightforward and can guide preoperative interventions to improve surgical outcomes. Polypharmacy for example, the use of multiple medications, is a known risk factor in elderly patients for impaired physical functioning, decreased postoperative survival and increased risk of complications and mortality.[20-22] The relationship between frailty, multi-morbidity, older age and polypharmacy is complex (**Figure 2**).[23]

Older people are the main users of medications as a result of multi-morbidity, and polypharmacy appears to increase the risk of frailty.[23] Besides, it is unclear whether frailty is a cause or consequence of multi-morbidity and there is an increasing recognition that biological changes of frailty affect pharmacokinetics and pharmacodynamics.[23]

Hence, disease-drug and drug-drug interactions can lead to heterogeneity in medication responses and increased adverse drug effects.[7,24] Polypharmacy also contributes to medication non-adherence, for example resulting in a suboptimal effect of prescribed analgesic perioperative pain management and more postoperative pain.[25] Unfortunately, the risk of postoperative pain is high in cardiac surgery patients and chronic postoperative pain affects 37% of patients in the first 6 months after surgery.[26] Moreover, patients after cardiac surgery with controllable pain, recover faster and have lower risk of postoperative complications.[27] Identifying preoperative risk factors such as polypharmacy and providing individualized perioperative pain treatment in frail elderly are both examples of perioperative risk management to improve surgical outcome.

Figure 2. Complex relationship between frailty, multi-morbidity, ageing and polypharmacy.



Bridging the gap between ICU and the surgical ward: risk monitoring of frail elderly patients

Given the significance of identifying risk factors to enhance postoperative care, it is essential to note that nearly half of all adverse events in hospitalized patients commonly arise in the early postoperative recovery phase at the general ward.[28-30] In addition, the European Surgical Outcomes Study[31] (EuSOS) stated that about three quarters of post-surgery in-hospital deaths occurred without intensive care unit admission, emphasizing the substantial risk inherent to general wards in postoperative patient care.

The failure to identify and act on physiological signs of deteriorating patients is a longstanding issue that was recognized over a decade ago.[32] To improve early recognition and adequate treatment for deteriorating patients, the (modified) early warning score (MEWS) was implemented.[33] The MEWS is measured by nurses and enables to differ between normal physiological changes and pathologic variation in vital signs. In case of deterioration, this score leads to intensification of monitoring, activation of rapid response teams and/or therapeutic interventions. Nowadays, intensive monitoring on the ward is limited and clinicians rely on intermittent spot checks using MEWS by nurses usually once every 6 – 8 hours.[34] This leaves patients unmonitored for most of the time and patients can deteriorate between observation sets. For example, in hospitalized patients recovering from non-cardiac surgery, one third of patients experienced severe hypoxemia (SpO_2 < 90% for one hour or more) and the occurrence and duration was seriously underestimated with spot check monitoring by nurses.[35] A different study regarding the systematic measurement of vital signs in patients on the general ward, demonstrated that completeness of MEWS in the first 3 days after major surgery was only 17%.[36] This calls into question whether intermittent spot check monitoring is adequate to address the changing profile of patients on general wards today. Increasing the intensity of spot checks by nurses may seem a sensible solution, but is unlikely given the fact that manual measurements are time-consuming and health personnel and hospital budgets are limited.

Empowering the surgical ward: the promise of continuous monitoring

Continuous monitoring of vital signs is a promising approach to early identify the deteriorating patient. Although complications often become clinically apparent as acute cardiac or respiratory failure, it has long been known that subtle abnormalities in vital signs typically precede these conditions, sometimes by 6 – 12 hours.[34,37] A recent meta-analysis evaluated the effect of continuous monitoring in general wards and indicated a 39% lower risk of mortality among continuously monitored patients compared to those receiving standard care (spot checks).[37] Furthermore, continuous monitoring was associated with a reduced need for patient rescue events,

reduced intensive care unit transfers and a reduced length of stay.[37] While continuous monitoring is not yet the standard of care, the technology for vital signs monitoring is advancing rapidly and promising. Especially in frail elderly patients, who are less resilient and more prone to adverse drug effects and postoperative complications, postoperative monitoring of vital signs may have the potential to early detect clinical deterioration. However, evidence for the effectiveness of continuous monitoring of vital signs in identifying postsurgical patients at risk is still scarce. We aimed to determine risk factors for postoperative deterioration at the general ward in frail elderly patients following cardiac surgery, using continuous monitoring.

Titration of analgesic medication in the frail elderly patient to reduce complications following cardiac surgery

The Anesthesia Patient Safety Foundation recommended already a decade ago that "Continuous electronic monitoring of oxygenation and ventilation would reduce the likelihood of unrecognized clinically significant opioid-induced depression of ventilation in the postoperative period".[38] Postoperative administration of opioids is essential in preventing and managing postoperative pain. However, the significant variation in how individuals respond to opioid doses complicates treatment to ensure safe and efficient pain relief. The challenges surrounding prescription of these high risk medications in older people are further amplified in the presence of frailty, as there is few data to support evidence-based decisions in such patients.[7,39] Moreover, opioid therapy in the elderly is often associated with adverse effects because of excessive respiratory depression.[7] The risk of clinically significant respiratory depression for hospitalized patients in their seventh, eight, and ninth decades of life is respectively 2.8, 5.4 and 8.7 times higher, than for younger patients.[39] Therefore, most opioid dosing regimens, especially in elderly patients or patients with limited physiologic reserves (e.g. frailty), tend to lean towards smaller doses or longer intervals, often leading to insufficient dosing. Consequently, the fundamental question arises "What is the correct dose for this frail elderly patient"?

Optimal pain control is a multifaceted and intricate challenge but essential given the high demand for analgesia in these patients following cardiac surgery. As the global population ages and frailty becomes more prevalent, understanding the pathophysiological mechanisms, including pharmacokinetics and pharmacodynamics in frail elderly patients, and their impact on drug therapy is essential. With this knowledge, it might be possible to facilitate customized care for every frail elderly patient following cardiac surgery. Additionally, implementing continuous monitoring for early detection of clinical deterioration at the general ward, might offer a secure environment for the administration of medication in this high risk population.

Therefore, this thesis will study novel risk factors for postoperative complications and poor functional outcomes using systematic analysis of continuous monitoring data and pharmacokinetic models collected in a high-risk surgical population.

Objectives of this thesis

I. To better understand the relationship between frailty domains, especially polypharmacy, and postoperative functional outcome after cardiac surgery.
II. To study the clinical utility of continuous postoperative monitoring of vital signs after ICU discharge in relation to early signs of clinical deterioration and side effects of high risk medication.
III. To study the pharmacokinetics and analgesic response of morphine in frail elderly patients following cardiac surgery, to identify strategies for safer medication use.

Outline of this thesis

Chapter 2 describes the association of polypharmacy with functional decline in frail elderly patients following cardiac surgery. **Chapter 3** assesses which preoperative frailty domains are associated with chronic pain and functional outcome one year after cardiac surgery in older patients. In **chapter 4** the association between vital signs and clinical deterioration using continuous remote monitoring on the general ward in frail elderly patients after cardiac surgery is prospectively studied. **Chapter 5** describes the effects of high risk medication on postoperative vital signs in frail elderly cardiac surgery patients, using continuous monitoring. In **chapter 6** we report the analysis of the pharmacokinetics and analgesic response of morphine treatment in frail older cardiac surgery patients. Lastly, in **chapter 7**, the results and overall conclusions of this thesis are summarized and discussed. In this chapter, perspectives are given concerning perioperative management in frail elderly patients. Finally, ideas are provided for further interventions or studies regarding optimizing patients safety and clinical outcome.

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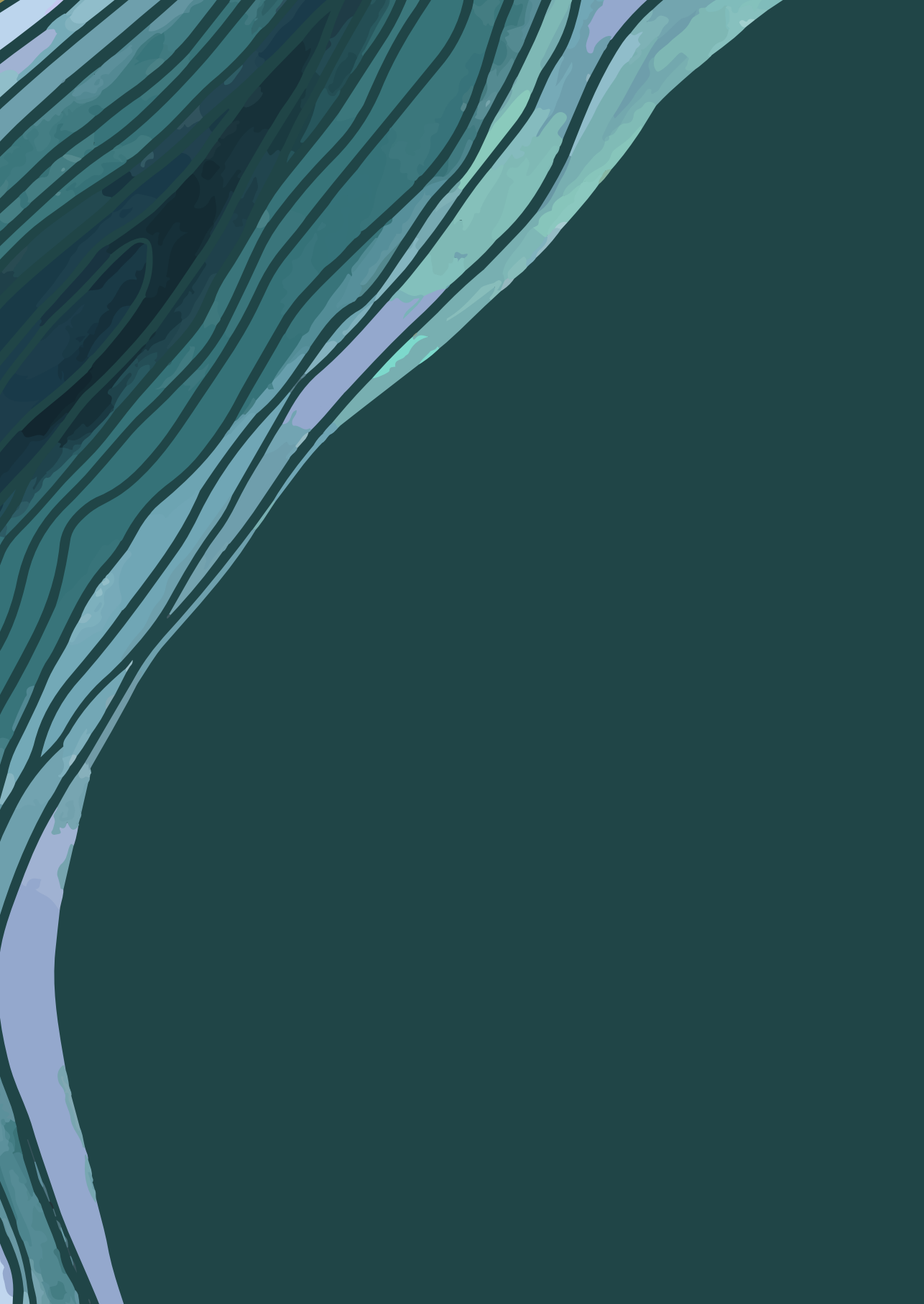

Chapter 2

The association of polypharmacy with functional decline in elderly patients undergoing cardiac surgery

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ABSTRACT

Background

Identifying preoperative risk factors in older patients becomes more important to reduce adverse functional outcome. This study investigated the association between preoperative medication use and functional decline in elderly cardiac surgery patients and compared polypharmacy as a preoperative screening tool to a clinical frailty assessment.

Methods

This sub-study of the Anaesthesia Geriatric Evaluation study included 518 patients ≥ 70 years undergoing elective cardiac surgery. The primary outcome was functional decline, defined as a worse health related quality of life or disability one year after surgery. The association between polypharmacy (i.e. ≥5 prescriptions and <10 prescriptions) or excessive polypharmacy (i.e. ≥10 prescriptions) and functional decline was investigated using multivariable Poisson regression. Discrimination, calibration and reclassification indices were used to compare preoperative screening tools for patient selection.

Results

Functional decline was reported in 284 patients (55%) and preoperative polypharmacy and excessive polypharmacy showed higher risks (aRRs 1.57, 95% CI 1.23 – 1.98 and 1.93, 95% CI 1.48 – 2.50, respectively). Besides cardiovascular medication, proton pomp inhibitors and central nervous system medication were significantly associated with functional decline. Discrimination between models with polypharmacy or frailty was similar (AUC 0.67, 95% CI 0.61 – 0.72). The net reclassification index improved when including polypharmacy to the basic model (17%, 95% CI 0.06 – 0.27).

Conclusion

Polypharmacy is associated with functional decline in elderly cardiac surgery patients. A preoperative medication review is easily performed and could be used as screening tool to identify patients at risk for adverse outcome after cardiac surgery.

INTRODUCTION

Polypharmacy is the use of an excessive number of drugs, often defined as the use of five or more different drugs by one individual.[1] It is a highly prevalent condition in the ageing population, as older people often suffer from chronic comorbidities. Across Europe, approximately one third of patients over 65 year has polypharmacy to treat underlying disease.[2] In the non-surgical population and after major elective non-cardiac surgery, polypharmacy is associated with increased poor functional status, decreased postoperative survival, unplanned hospital admissions, increased risk of complications and mortality.[1,3,4] However, the prevalence of polypharmacy and the association with adverse functional outcomes in patients undergoing cardiac surgery is poorly described.

In recent years, an increasing number of studies has demonstrated the association between frailty and adverse outcome in the surgical population.[5,6] Since the population ages and the number of elderly requiring cardiac surgery is rising, identifying preoperative risk factors becomes more important in an attempt to reduce adverse functional outcome. There is growing evidence suggesting that a preoperative comprehensive frailty assessment can improve risk stratification in older cardiac surgery patients.[6–8] However, a comprehensive frailty assessment is time consuming. Polypharmacy is easily identified in surgical patients as a systematic assessment of prescribed drugs, which is part of routine preoperative care.

We hypothesized that a preoperative screening for polypharmacy can be used to easily identify cardiac patients with increased risk of adverse functional outcome. This may improve risk stratification before surgery, without additional patient burden, and facilitate targeted preoperative interventions. The aim of this study was to evaluate the association of polypharmacy with functional decline after cardiac surgery. Additionally, we identified commonly used drugs that are associated with functional decline. Our secondary aim was to evaluate polypharmacy as a preoperative screening tool for adverse functional outcome, compared to a clinical frailty assessment.

METHODS

Study design and population

This study reports the results of a post hoc analysis of the Anaesthesia Geriatric Evaluation and Quality of Life After Cardiac Surgery (AGE) study and analysed patients included at St. Antonius Hospital, the Netherlands.[7] The AGE study was a prospective observational cohort study in patients aged 70 years and older, that focused on the association between preoperative frailty domains and health related quality of life (HRQL) and disability after one year in elective cardiac surgery patients (i.e. coronary, valve, rhythm, aortic, or any combination of these procedures). The local ethics committee approved the study protocol before patient recruitment (Medical Ethics Research Committee United, number R15.039), which was registered at clinicaltrials.gov under NCT02535728. All participants provided written informed consent. Inclusion took place from July 2015 until August 2017. Details of the objectives, design and methods of the AGE study were published previously.[7]

Clinical characteristics and data collection

Demographics and medical history were derived from the electronic health record, including health status, comorbidities, previous surgical procedures and/or laboratory tests. After routine preoperative anaesthesia screening, eleven frailty domains were assessed in all study patients. Nutritional status was assessed with the Mini Nutritional Assessment[9] (MNA), gait speed with the Timed Get Up & Go test[10] (TGUG) and five-meter gait speed test[6] (5-ML), daily functioning with the NAGI scale[6], a handgrip strength test[11] (GRIP) and analysis of polypharmacy. To assess cognition the Minimal Mental State Examination[12] (MMSE) was used and HRQL was assessed using the Short Form-36 questionnaire (SF-36).[13,14] Further screening included an evaluation of living situation and educational status. An elaborate description of frailty tests and chosen cut-off values is described in **Supplementary Table 1**. Postoperative complications were graded according to severity by members of the AGE research team.[7] A severe complication was defined as in-hospital mortality or a life-threatening event and included; re-operation, respiratory insufficiency, reintubation, stroke, renal replacement therapy, life threatening bleeding, or re-admittance to the intensive care unit.[7]

Medication characteristics

Before preoperative anaesthesia screening, all patients were subjected to a routine medication review by a hospital pharmacist. Polypharmacy and excessive polypharmacy were defined as ≥ 5 and <10 different type of prescriptions and ≥ 10 different type of prescriptions, respectively.[1] Preoperative medications were divided into groups, based on the Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to

Alert to Right Treatment (START) criteria[15], mechanism of action and clinical importance. These were as follows: "Beta-blockers", "Digoxin", "Antihypertensives", "Diuretics", "Statins", "Anticoagulants", "Central Nervous System (CNS) medication", "Inhalation medication", "Cortico-immunosuppressives", Antidiabetics", "Proton Pomp Inhibitors (PPIs)", and Non-Steroid Anti-Inflammatory Drugs (NSAIDs)". Antihypertensives included calcium-antagonists, angiotensin converting enzyme inhibitors and angiotensin-2 antagonists. Anticoagulants consisted of platelet aggregation inhibitors, dual anti platelet therapy, new/direct anticoagulants, vitamin K antagonists and low molecular weight heparin. CNS medication included benzodiazepines, selective serotonin reuptake inhibitors, tricyclic antidepressants and non-tricyclic antidepressive medication. Inhalation medication included inhalation corticosteroids and inhalation parasympathicolytics and sympathicomimetics or a combination of these.

Outcomes

The primary outcome of this study was functional decline, defined as worse HRQL or disability one year after surgery. HRQL was surveyed with the SF-36 and summarized into a physical HRQL and mental HRQL score. Worse HRQL was defined as a decrease of ≥5 points in physical or mental HRQL score after one year compared to HRQL prior to surgery.[16] Disability was assessed by the 36-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0).[17] A score of ≥25% represented disability, death was scored as maximum disability (100%).[7,18]

Statistical analysis

Data are presented as frequencies and percentages (%) for dichotomous and categorical data and for continuous data as median with interquartile range (IQR) or mean with standard deviation (SD), as appropriate. Continuous data were checked on normality with visual inspection of the histograms and Q-Q plots. Patients with and without polypharmacy and excessive polypharmacy one year after surgery were compared using the Chi square test for dichotomous or categorical variables or the One-Way ANOVA test or Kruskal-Wallis Test for continuous variables, as appropriate. To investigate the association between polypharmacy and functional decline, Poisson regression analysis with robust standard errors was used to present effect estimates as risk ratios (RR) with accompanying 95% confidence interval (CI). As functional decline after cardiac surgery was relatively common, the rare disease assumption would not hold. This means that an odds ratio, would not approach the corresponding risk ratio, hampering the interpretation of our results for clinical practice.[19] The association was adjusted for a priori selected confounders based on the results from the previously published AGE studies and prior knowledge obtained from literature. These comprised sex, age, type of surgery, and frailty characteristics including living alone, TGUG and

NAGI physical functioning.[6,7,20] The association between different types of medication and functional decline was analysed in a similar manner.

To evaluate polypharmacy as screening tool for functional decline, and compare to a clinical assessment of the frailty characteristics, three models were developed using multivariable logistic regression analysis. A basic model included sex, age, type of surgery, and the extensive models additionally included polypharmacy with excessive polypharmacy or the aforementioned selected frailty characteristics to the basic model. Models were compared using the likelihood ratio test (LRT). Receiver operation characteristic (ROC) curve analyses were performed to assess the discriminatory strength of each model [area under the curve (AUC); 95% CI]. The Hosmer-Lemeshow test was assessed as a measure of overall calibration. Thereafter, the ability of reclassification for each model was evaluated by net reclassification improvement (NRI) using the proportions of patients reclassified to a different risk group based on a model with polypharmacy and excessive polypharmacy or frailty characteristics, compared to the basic model.[21,22] Patients were classified into low, intermediate and high risk groups of functional decline (<40%, 40–60% and ≥60%). The sum of correct reclassifications was expressed as total NRI.[21,22] Integrated discrimination improvement (IDI) represents a category free-measure for reclassification by an additional risk maker and follows the principles of NRI analysis.[21,22] It quantifies the net improvement in correct mean predicted event probabilities. As functional decline was missing for 15% of cases and could lead to potential bias, multiple imputation was conducted using the mice library (R version 3.6.3, 2020).[23] Twenty datasets were created and the estimates and variances for each of the imputed datasets were pooled into an overall estimate using Rubin's rule.[23,24] For the NRI and IDI the median and the IQR of all indices obtained from the twenty imputed datasets was used. The imputed dataset was used for final analysis. P-values of ≤ 0.05 were considered statistically significant. Data analysis was performed using R statistics (version 3.6.3, 2020).

RESULTS

Study population

This cohort included 518 (95%) patients out of 544 eligible for analysis in the AGE study. Reasons for exclusion were withdrawal (n=9) or cancellation of surgery (n=17). In 81 patients imputation of missing values was performed. Baseline characteristics between patients with and without missing data were not different (**Supplementary table 2**). Median age was 74 years (IQR 72–77) and 349 patients (67%) were male. The most common comorbidities were hypertension (85%), renal failure (35%) and diabetes mellitus (21%). The median number of medications was six (IQR 4 – 8). The prevalence of polypharmacy (i.e. ≥5 drugs) was 67% (n=345), of whom 26% (n=88) had excessive polypharmacy (i.e. ≥10 drugs). Commonly used medications in patients with polypharmacy were cardiovascular medication such as anticoagulants (92%), antihypertensives (88%), statins (75%) and beta-blockers (71%). The most frequently used non-cardiovascular medications in the polypharmacy group were PPIs (61%), anti-diabetics (27%) and CNS medication (18%). Patients with excessive polypharmacy had a higher EuroSCORE II and the median number of prescribed medications was 11 (IQR 10 – 12). Baseline characteristics according to polypharmacy are presented in **Table 1**.

Table 1. Baseline (n = 518).

	No polypharmacy (n = 173)	**Polypharmacy** (n = 257)	**Excessive polypharmacy** (n = 88)	**P-value**
Patient characteristics				
Male sex	115 (67)	171 (67)	63 (72)	0.65
Age (y)	74 (72 – 77)	75 (72 – 78)	74 (72 – 77)	0.80
EuroSCORE II	1.54 (1.14 – 2.40)	1.87 (1.25 – 3.39)	2.51 (1.46 – 4.29)	< 0.001
LVEF < 50%	21 (12)	57 (22)	26 (30)	< 0.01
Prescriptions				
Beta-blockers	65 (38)	180 (70)	65 (74)	< 0.001
Digoxin	8 (5)	21 (8)	6 (7)	0.36
Antihypertensives	75 (43)	222 (86)	81 (92)	< 0.001
Diuretics	45 (26)	122 (48)	53 (60)	< 0.001
Statins	67 (39)	195 (76)	65 (74)	< 0.001
Anticoagulants	106 (61)	234 (91)	83 (94)	< 0.001
CNS medication	8 (5)	32 (13)	30 (34)	< 0.001

Table 1. Baseline (n = 518). (continued)

	No polypharmacy (n = 173)	Polypharmacy (n = 257)	Excessive polypharmacy (n = 88)	P-value
Inhalation medication	9 (5)	31 (12)	27 (31)	< 0.001
Cortico-immunosuppressives	1 (1)	11 (4)	14 (16)	< 0.001
Antidiabetics	7 (4)	52 (20)	41 (47)	< 0.001
PPIs	29 (17)	145 (56)	67 (76)	< 0.001
NSAIDs	2 (1)	11 (4)	10 (11)	0.001
Comorbidities				
Hypertension	111 (64)	241 (94)	87 (99)	< 0.01
COPD	5 (3)	25 (10)	29 (33)	< 0.01
Diabetes Mellitus	8 (5)	58 (23)	43 (49)	< 0.01
Renal Failure	49 (28)	92 (36)	39 (44)	0.03
Preoperative laboratory tests				
Haemoglobin (mmol L^{-1})	8.80 (8.30 – 9.40)	8.70 (8.10 – 9.20)	8.40 (7.68 – 9.20)	< 0.01
Creatinine (µmol L^{-1})	88 (75 – 99)	88 (76 – 106)	92 (77 – 115)	0.05
Albumin (g L^{-1})	43.85 (41.80 – 45.38)	43.50 (41.70 – 45.20)	42.70 (41.50 – 44.60)	0.04
Intraoperative characteristics				
Type of surgery				
Single CABG or maze	31 (18)	108 (42)	40 (46)	< 0.001
Single valve	73 (42)	52 (20)	19 (22)	< 0.001
Combined surgery	56 (32)	79 (31)	21 (24)	0.35
Aortic surgery	13 (8)	18 (7)	8 (9)	0.82
Duration of surgery (min.)	196 (161 – 256)	239 (163 – 250)	217 (180 – 267)	0.19
Postoperative characteristics				
Length of stay in the ICU (days)	1 (1 – 2)	1 (1 – 2)	1.5 (1 – 4)	< 0.01
Length of hospital stay (days)	8 (7 – 12)	9 (7 – 13)	10 (8 – 16)	< 0.01
Severe complication	33 (19)	42 (17)	22 (27)	0.18

Continuous values as mean (± standard deviation) or median (1st to 3rd quartile), categorical values as frequency (%). n: number; y: years; LVEF: left ventricular ejection fraction; CNS: central nervous system; PPIs: proton pomp inhibitors; NSAIDs: non-steroid anti-inflammatory drugs; COPD: chronic obstructive pulmonary disease; CABG: coronary artery bypass grafting; ICU: intensive care unit. Polypharmacy was defined as ≥5 and <10 and excessive polypharmacy was defined as ≥10 different type of prescriptions used.

The association between polypharmacy and functional decline

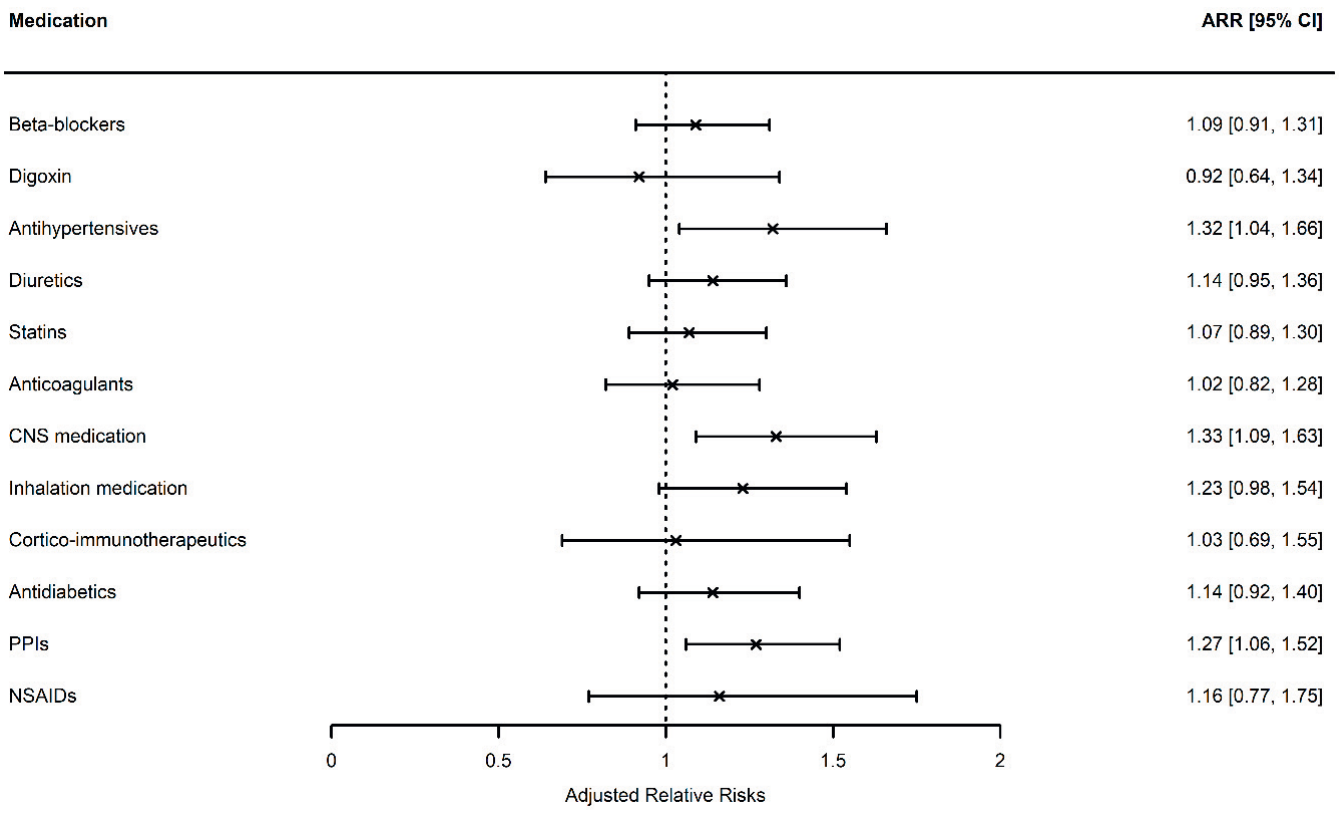
A total of 284 patients (55%) had functional decline one year after surgery, of which 63% was caused by disability and 37% due to worse HRQL. Patients with excessive polypharmacy had the highest incidence of functional decline (73%), compared to patients with polypharmacy (58%) and patients without polypharmacy (42%), p-value < 0.001. After adjustment for age, sex and type of surgery, polypharmacy and excessive polypharmacy showed higher relative risks of functional decline (adjusted relative risk (aRR) 1.57, 95% CI 1.23 – 1.98; aRR 1.93, 95% CI 1.48 – 2.50, respectively). Besides cardiovascular medication, PPIs, inhalation and CNS medication were significantly associated with functional decline (**Figure 1**). After including frailty characteristics to the model, diuretics and inhalation medication were no longer associated with functional decline.

Preoperative risk stratification based on polypharmacy

Risk stratification for functional decline one year after cardiac surgery based on age, sex and type of surgery was poor (AUC 0.62, 95% CI 0.56 – 0.67). Discrimination improved by adding polypharmacy and excessive polypharmacy (AUC 0.67, 95% CI 0.61 – 0.72) and was similar to a model that included frailty. None of the models showed statistically significant overall miscalibration (**Table 2**).

To assess the incremental prognostic value of (excessive) polypharmacy, the predicted risk for functional decline was recalculated after addition of (excessive) polypharmacy to the basic model (**Table 3**). In patients with functional decline (n=238), addition of (excessive) polypharmacy to the basic model resulted in 73 (31%) patients that were correctly reclassified and 37 (16%) patients that were incorrectly reclassified. In patients without functional decline (n=280), 55 (20%) patients were correctly assigned to a lower risk category and 52 (18%) patients were incorrectly reclassified. The total NRI in our final model, including polypharmacy and excessive polypharmacy, was 17% (95% CI 0.06 – 0.27). Meaning, one in five patients was correctly reclassified to a different risk category after stratification based on (excessive) polypharmacy, compared to the basic model with age, sex and type of surgery alone. The IDI quantifies the net improvement in correct mean predicted event probabilities and revealed a higher predictive accuracy for a model including (excessive) polypharmacy compared to the basic model (IDI 0.04, 95% CI 0.02 – 0.06, **Table 3**).

Figure 1. Adjusted relative risk on functional decline per medication prescription.



CI: confidence interval; CNS: central nervous system; PPIs: proton pomp inhibitors; NSAIDs: non-steroid anti-inflammatory drugs. Poisson regression analysis was used for statistical testing with correction for age, sex, type of surgery; p-value ≤0.05 was considered statistically significant.

Table 2. Calibration and discrimination of the different models.

Model	AUC (95% CI)	Goodness-of-fit (p)
Basic model	0.62 (0.56 – 0.67)	p = 0.96
Basic model + polypharmacy + excessive polypharmacy	0.67 (0.61 – 0.72)	p = 0.93
Basic model + frailty characteristics	0.67 (0.62 – 0.72)	p = 0.44

AUC: area under the curve; CI: confidence interval. Polypharmacy was added as factor with polypharmacy defined as ≥5 and <10 and excessive polypharmacy defined as ≥10 different type of prescriptions used. No polypharmacy was used as reference category. To assess goodness-of-fit a Hosmer-Lemeshow test was performed.

Table 3. Net reclassification improvement analysis.

	Basic model + polypharmacy and excessive polypharmacy					
NRI scores	*Patients without functional decline*			*Patients with functional decline*		
	< 40%	40 – 60%	40 – 60%	< 40%	40 – 60%	40 – 60%
< 40%	71	32	0	29	30	0
40 – 60%	49	90	20	24	79	43
> 60%	0	6	12	0	13	20

The NRI reclassifies the patients into different risk groups. In patients with functional decline (n=238), addition of (excessive) polypharmacy to the basic model resulted in 73 (31%) patients (green) that were correctly reclassified and 37 (16%) patients (purple) incorrectly reclassified. In total 31-15=15% of patients with functional decline were correctly reclassified, when (excessive) polypharmacy was added to the basic model. In patients without functional decline (n=280), 55 (20%) patients were correctly assigned to a lower risk category (green) and 52 (18%) patients were incorrectly reclassified (purple). This means that in total 20-18 = 2% of patients without functional decline were correctly reclassified when (excessive) polypharmacy was added to the basic model. The total NRI improvement was 17% (15+2%). Green: correct reclassification; white: no change; purple; incorrect reclassification. Results are shown from a randomly picked single imputed dataset.

DISCUSSION

In this cohort study of patients aged 70 years or older, preoperative polypharmacy and excessive polypharmacy were associated with functional decline one year after cardiac surgery. Besides cardiovascular medication, PPIs and CNS medication demonstrated significantly higher relative risks for adverse outcome. A model including polypharmacy improved preoperative risk classification and might be used as screening tool to identify high risk patients for cardiac surgery.

Consistent with the literature in non-cardiac surgery patients, we found in cardiac surgery patients that polypharmacy is associated with negative postoperative outcomes.[3,4,25] McIsaac et al. demonstrated that patients with polypharmacy having major elective non-cardiac surgery had decreased postoperative survival, increased rates of complications, and higher resource use.[4] By comparison, we found that patients with polypharmacy or excessive polypharmacy had significantly higher relative risks of functional decline one year after surgery, compared to those without (1.49 and 1.82 respectively, $p < 0.001$). Since patients who take more medications are likely to have poorer health, true causation cannot be established due to confounding. On the other hand, adjustment for chronic conditions might lead to overcorrection considering the fact that polypharmacy represents comorbidities. Although a prospective study with accurate adjustment for baseline illness is required to assess the causal relationship, it remains clear that there is an association between polypharmacy and adverse postoperative outcomes. A possible explanation is that with an ageing population and increase in multimorbidity, the number of drugs will exponentially increase, which in turn increases the risk of adverse events. Especially elderly are at greater risk due to metabolic changes and decreased drug clearance associated with ageing.[26,27] Additionally, polypharmacy enhances the potential for drug-drug interactions, leading to adverse outcomes.

In depth analysis identified commonly used cardiovascular drugs as high risk medication for adverse outcome. Besides cardiovascular medication, patients using CNS medications or PPIs were at higher risk for the development of functional decline one year after cardiac surgery. Several studies have examined ways for deprescribing to improve outcomes and refer to consensus lists such as Beers criteria or the STOPP criteria.[15,28] Commonly used medications on these lists include benzodiazepines, benzodiazepine receptor agonists and chronic use of PPIs. Recent studies regarding the long-term use of PPIs have noted potential adverse effects, including risk of fractures, pneumonia, diarrhoea, hypomagnesemia, vitamin B12 deficiency, chronic kidney disease and dementia.[29] In addition, CNS medication, including benzodiazepines

and antidepressants can lead to an increased risk of falls and severe sedation-related adverse events such as respiratory depression and death.[15,28,30] In this study, patients preoperatively using CNS medication or a PPI had a 30% and 34% higher risk to develop functional decline one year after surgery. These results demonstrate that a medication review before surgery is preferable to identify patients at risk for functional decline and deprescribe if possible. Although the use of cardiovascular drugs in our specific cardiac surgical population is inevitable, CNS or PPIs prescriptions can be reconsidered.

Apart from the association, we evaluated polypharmacy as screening tool for adverse functional outcome, compared to a clinical frailty assessment. Existing literature in non-cardiac surgery patients indicates that older patients with polypharmacy represent a high-risk stratum of the perioperative population.[4] Additionally, there is growing evidence suggesting that a preoperative comprehensive frailty assessment can improve risk stratification in older cardiac surgery patients.[6–8] The relationship between polypharmacy and frailty is still unclear, but they are both associated with adverse postoperative outcome.[1,3–6] As polypharmacy is easily identified and a medication review is part of routine preoperative screening, we suggest that perioperative clinicians first assess polypharmacy. Thereafter frailty assessments can be considered to identify older high-risk cardiac surgery patients who may benefit from preoperative shared decision-making and a personalised perioperative treatment plan.

This study has several limitations. First, in 81 patients HRQL or disability was missing. Eventually, comparison between patients with complete cases and patients with missing values showed no differences and imputation of missing values was performed. Second, this study was not specifically designed to evaluate polypharmacy. Our definition of polypharmacy was a categorisation of a continuous variable and did not account for the potential differing risk impacts of different drugs in elderly patients. Also, medication adherence was not specifically assessed. Third, we were not able to frame a prediction model, due to the retrospective design of this post hoc analysis. The net benefit was only used to quantify the clinical usefulness of these screening tools, but for future implementation in clinical decision making it is important that a specific prediction model is developed.

In conclusion, preoperative polypharmacy and excessive polypharmacy are easily identified and significantly associated with functional decline in older patients one year after cardiac surgery. More specifically, besides cardiovascular medication, CNS medication and PPIs showed significantly higher relative risks for adverse outcomes. Screening for polypharmacy at an early stage might help to identify elderly patients

at risk for functional decline after cardiac surgery. Individual medication reviews and preoperative drug optimization might be a first step in perioperative optimization, where after additional frailty assessments and prehabilitation trajectories can be considered.

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Supplementary table 1. Description of frailty domains in the anaesthesia geriatric frailty evaluation.

Frailty domain	Test	Method of assessment	Cut off value
Nutritional status	Mini nutritional assessment	Six item questionnaire on weight loss, eating, BMI, and psychological status	A score ≤11 out of 14 identified patients at risk for malnutrition[9]
Gait speed	5-meter walk test	Patients were instructed to walk at their normal pace with walking aids if needed for five meters. Time between first footfall after the starting line and first footfall after the five meter line was recorded	Impaired gait speed was defined as ≥6 seconds or inability to perform the test[6]
	Timed get up and go test	Time was recorded between standing up from a seated position in a chair, walk for three meters with walking aids if needed and return to a seated position	Impaired gait speed was defined as ≥10 seconds or inability to perform the test[10]
Polypharmacy	Number of prescriptions	Assessment by hospital pharmacy services	≥5 and <10 different type of prescriptions ≥10 different type of prescriptions (excessive)[1]
Daily functioning	Nagi's scale of physical disability	Seven item questionnaire on lifting heavy objects, kneeling, raising arms above the head, walking one flight of stairs, and walking 1.5 kilometres	A score ≥3 implied impairments[6]
Handgrip strength	Hydraulic handheld dynamometer	Best result of three consecutive tests to squeeze dynamometer with lower arm unsupported and in 90° angle.	According to age and sex[11]
Cognition	Mini Mental State Examination	Eleven item questionnaire on orientation in time and place, short term memory, attention, and following verbal and written commands.	A score of ≤25 out of 30 was considered as mildly impaired cognition[12]
Health related quality of life	Medical Outcomes Study Short Form 36	36 item self-assessed questionnaire on physical and mental well-being generating two scores representing mental and physical health related quality of life	A deviation of >1 standard deviation from the population mean was considered impaired[13,14]
Living situation	Interview		Impaired when a patient was living without a partner or family
Educational status	Interview		Impaired when no education beyond secondary education was followed

BMI: body mass index.

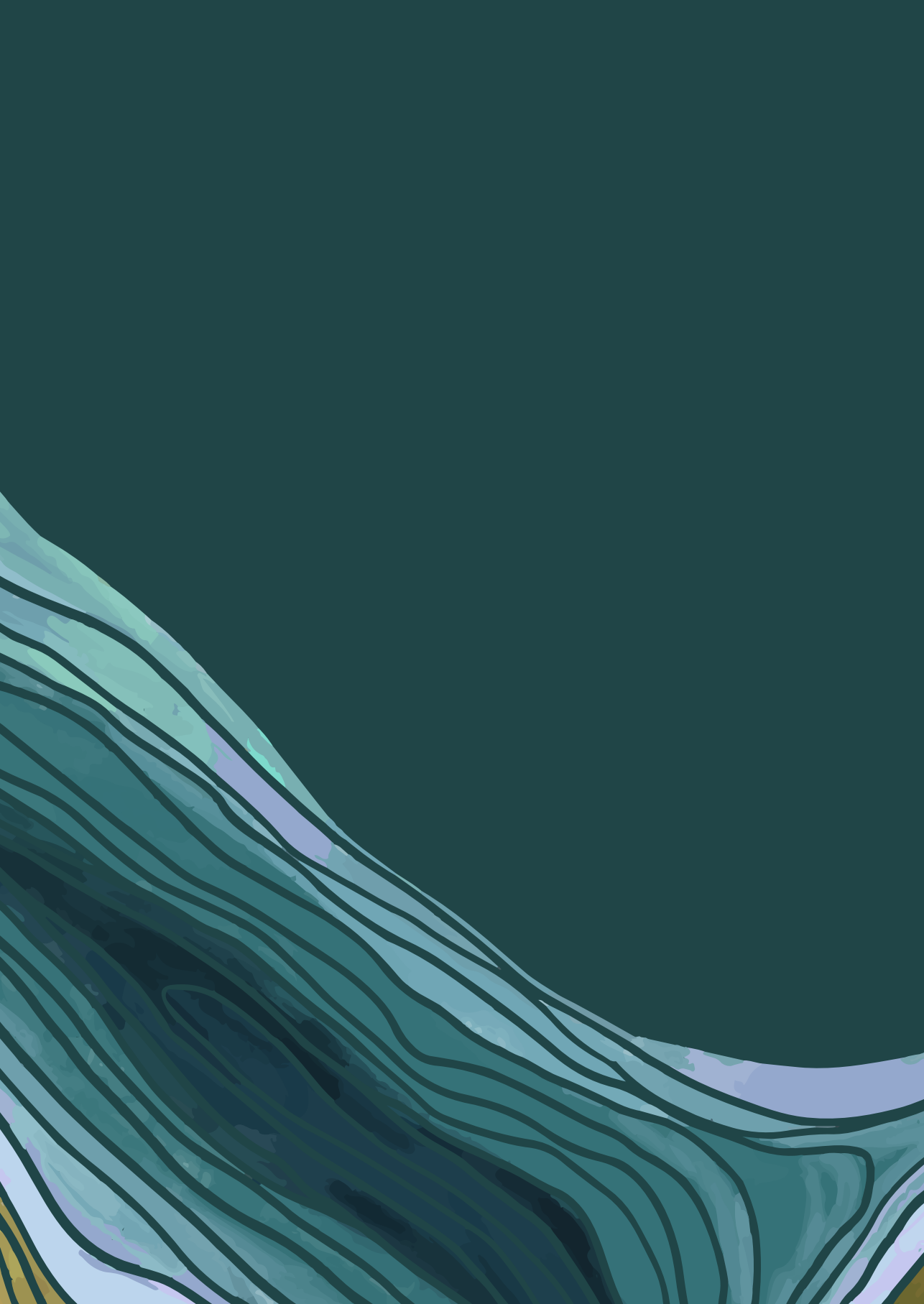
Supplementary table 2. Baseline for patients with and without missing data.

	With missing data (n = 81)	Without missing data (n = 437)	P-value	Missings
Patient characteristics				
Male sex	52 (64)	297 (68)	0.59	0
Age (y)	75 (72 – 78)	74 (72 – 77)	0.20	0
EuroSCORE II	2.15 (1.39 – 2.95)	1.81 (1.22 – 3.28)	0.18	0
Living alone	23 (28)	87 (20)	0.12	0
LVEF < 50%	14 (17)	90 (21)	0.60	0
Polypharmacy				0
No polypharmacy	28 (35)	145 (33)	1	
Polypharmacy	39 (48)	218 (50)	0.91	
Excessive polypharmacy	14 (17)	74 (17)	1	
Comorbidities				
Hypertension	69 (85)	370 (85)	1	0
COPD	12 (15)	92 (21)	0.39	0
Diabetes Mellitus	17 (21)	92 (21)	1	0
Renal Failure	23 (28)	157 (36)	0.24	0
Preoperative laboratory tests				
Haemoglobin (mmol L-1)	8.60 (8.10 – 9.20)	8.70 (8.10 – 9.30)	0.43	0
Creatinine (µmol L-1)	88.00 (75.00 – 110)	89.00 (76.00 – 105.00)	0.89	0

Supplementary table 2. Baseline for patients with and without missing data. (continued)

	With missing data (n = 81)	Without missing data (n = 437)	P-value	Missings
Albumin (g L-1)	43.20 (41.55 – 44.92)	43.60 (41.80 – 45.30)	0.34	16
Intraoperative characteristics				
Type of surgery				
Single CABG or maze	24 (35)	151 (35)	1	0
Single valve	15 (19)	129 (30)	0.06	
Combined surgery	32 (40)	124 (28)	0.06	
Aortic surgery	6 (7)	33 (8)	1	
Duration of surgery (minutes)	216 (174 – 274)	205 (162 – 252)	0.11	0
Postoperative characteristics				
Length of stay in the ICU (days)	1 (1 – 2)	1 (1 – 2)	0.74	0
Length of hospital stay (days)	10 (7 – 14)	8 (7 – 13)	0.15	6
Severe complication	12 (16)	85 (20)	0.50	0

Continuous values as mean (± standard deviation) or median (1st to 3rd quartile), categorical values as frequency (%). n: number; y: years; LVEF: left ventricular ejection fraction; CNS: central nervous system; PPIs: proton pomp inhibitors; NSAIDs: non-steroid anti-inflammatory drugs; COPD: chronic obstructive pulmonary disease; CABG: coronary artery bypass grafting; ICU: intensive care unit. Polypharmacy was defined as ≥5 and <10 and excessive polypharmacy was defined as ≥10 different type of prescriptions used.



Chapter 3

Preoperative frailty and chronic pain after cardiac surgery:

a prospective observational study

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ABSTRACT

Background

Chronic pain after cardiac surgery, whether or not related to the operation, is common and has negative impact on health related quality of life (HRQL). Frailty is a risk factor for adverse surgical outcomes, but its relationship with chronic pain after cardiac surgery is unknown. This study aimed to address the association between frailty and chronic pain following cardiac surgery.

Methods

This sub-study of the Anesthesia Geriatric Evaluation study included 518 patients ≥ 70 years undergoing elective cardiac surgery. Pain was evaluated with the Short-Form 36 questionnaire prior to and one year after surgery. Associations between chronic postoperative pain and frailty domains, including medication use, nutritional status, mobility, physical functioning, cognition, HRQL, living situation and educational level, were investigated with multivariable regression analysis.

Results

Chronic pain one year after cardiac surgery was reported in 182 patients (35%). Medication use, living situation, mobility, gait speed, Nagi's physical functioning and preoperative HRQL were frailty domains associated with chronic pain after surgery. For patients with chronic pain physical HRQL after one year was worse compared to patients without chronic pain (β 10.37, 99% CI −12.57 – −8.17).

Conclusion

Preoperative polypharmacy, living alone, physical frailty and lower mental HRQL are associated with chronic pain following cardiac surgery. Chronic postoperative pain is related to worse physical HRQL one year after cardiac surgery. These findings may guide future preoperative interventions to reduce chronic pain and poor HRQL after cardiac surgery in older patients.

INTRODUCTION

Chronic pain is a well-known complication after cardiac surgery and is reported by 18 to 35% of cardiac surgery patients in the Netherlands.[1-3] Especially in older patients, chronic pain, whether or not related to surgery, has a major impact on postoperative functional outcome, including health related quality of life (HRQL).[1-5] Physical inactivity and reduced self-reliance due to chronic pain, have been associated with a greater vulnerability to stressors, social isolation, anxiety and depression.[5-11] Although preoperative anesthesiological assessment routinely includes risk stratification for cardiac or pulmonary complications, standardized screening for the risk to develop chronic pain is less common. Given the negative effects, it is essential that risk factors for chronic pain after surgery are identified in order to initiate preventive strategies.

Frailty is characterized by a limited resilience to surgical stress, and has been associated with poor postoperative outcomes.[12-14] In community-dwelling elderly, chronic pain has been related to frailty.[13] Frail patients have more pain, poorer daily functioning and less physical activity.[13] In the surgical population, frailty has been associated with chronic pain after major elective non-cardiac surgery.[15] Although frailty is considered an important risk factor for poor surgical outcomes, evidence of a relationship between frailty and chronic pain following cardiac surgery is lacking. Identification of a relation between specific preoperative frailty characteristics (domains) and postoperative chronic pain may guide interventions to improve surgical outcome. With an ageing population, the number of cardiac surgery procedures in older patients will rise in the upcoming years.[4-6] Optimizing preoperative circumstances in these patients is therefore essential to target analgesic interventions and preserve postoperative quality of life. We hypothesized that preoperative frailty domains are associated with chronic pain and worse HRQL one year after cardiac surgery in older patients.

This study therefore aimed to address whether specific frailty domains are associated with chronic pain following cardiac surgery in an older population. Additionally, the relationship of chronic pain to HRQL was evaluated.

METHODS

Study design and population

This sub-study of the Anesthesia Geriatric Evaluation and quality of life after cardiac surgery (AGE) study analyzed patients included at St. Antonius Hospital, The Netherlands.[16,17] The AGE study was a prospective observational cohort study in patients aged 70 years and older, that focused on the association between preoperative frailty with HRQL and disability after one year in elective cardiac surgery patients (i.e. coronary, valve, rhythm, aortic, or any combination of these procedures). The medical ethics committee approved the study protocol before patient recruitment (Medical Ethics Research Committees United (www.mec-u.nl), number R15.039). The study was first registered at clinicaltrials.gov under NCT02535728 at 31/08/2015. This manuscript adheres to the applicable STROBE guidelines. All participants provided written informed consent. Details on design and analyses of the AGE study have been previously reported.[16]

Clinical characteristics and data collection

After routine preoperative screening, an additional geriatric assessment was performed to assess physical, mental and social frailty in eleven domains. Physical frailty included the following domains: medication use, nutritional status using the Mini Nutritional Assessment[18] (MNA), mobility and gait speed using the Timed Get Up & Go test[19] (TGUG) and five-meter gait speed test[20] (5-MWT), daily physical functioning using Nagi's scale[20] and a handgrip strength test.[21] Screening for mental frailty included cognition using the Minimal Mental State Examination[22] (MMSE) and self-rated mental and physical health with the Short-Form 36 questionnaire[23,24] (SF-36). To assess social frailty, we evaluated the living situation and educational level. Based on the multidimensionality of the frailty syndrome, a patient was considered 'overall frail' if a positive test for physical, mental and social frailty was present. An elaborate description of frailty tests and chosen cut-off values is described in additional **Supplementary table 1**. Demographics and medical history were derived from the electronic health record, including health status, comorbidities, previous surgical procedures and/or laboratory tests. Data from the SF-36 was used to identify presence of preoperative pain (see 'outcomes' section below). Information on preoperative use of analgesics was retrospectively collected from electronic patient files and included acetaminophen, non-steroid anti-inflammatory drugs (NSAIDs), opioids and antidepressants. Opioids included intravenous and subcutaneous administered morphine, oxycodone hydrochloride controlled-release (Oxycontin), oxycodone hydrochloride immediate-release (Oxynorm) and tramadol. Antidepressants were selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), pregabalin and amitriptyline.

Polypharmacy and excessive polypharmacy were defined as ≥ 5 and <10 prescriptions and ≥ 10 prescriptions, respectively.

Perioperative analgesia

Perioperative care was routinely performed according to local standard operating procedures. For intraoperative analgesia a continuous infusion of remifentanil was initiated directly after induction of anesthesia and intermittent fentanyl doses were used at predetermined times (i.e. prior to incision of the skin, sternotomy, aorta cannulation and opening of the pericardium). The dose of remifentanil and fentanyl was determined at the discretion of the attending anesthesiologist, depending on patient characteristics and intraoperative vital parameters. All patients received a loading dose of 10 mg intravenous morphine 30 minutes before the anticipated end of surgery. Postoperative pain management at the intensive care unit (ICU) consisted of intravenous paracetamol (1 g every six hours) and a continuous infusion of morphine (1-2 mg/h) according to protocol. After ICU discharge a standardized postoperative pain protocol was started including Oxycontin 10 mg twice daily, Oxynorm 5 mg as needed (maximum 6 times a day) and paracetamol 1 g four times a day during the first and second day at the ward. On the third day at the ward opioids were reduced and Oxynorm 5 mg as needed was prescribed, together with paracetamol 1 g four times a day. From the fourth day onwards patients received paracetamol 1 g four times a day. Insufficient pain control was managed by consultation of the hospital acute pain service that advised on an individualized pain treatment plan. Patients that suffered chronic pain preoperatively continued their pain therapy, with the exception of NSAID use. Preoperative opioid use was taken into account when defining postoperative opioid dose.

Outcomes

One year after cardiac surgery, study patients were invited by letter to complete and return the SF-36 questionnaire. One phone-call was used to remind non-responders. The primary outcome was chronic pain following cardiac surgery after 12 months. Data from the SF-36 questionnaires prior to and one year after surgery were used to determine chronic pain by the following question: 'How much bodily pain did you have during the past 4 weeks?' Answers were graded 1 to 6 and represented; 'None' (1), 'Very Mild' (2), 'Mild' (3), 'Moderate' (4), 'Severe' (5) and 'Very Severe' (6).[22,23] For this study, chronic pain was divided in three groups: 'No pain' (grade 1), 'Mild pain' (grade 2-3) and 'Moderate to severe pain' (grade 4-6). Chronic pain was defined as a reclassification into a higher grade of pain or no improvement of preexistent moderate to severe pain one year after cardiac surgery. The source or location of pain symptoms were not registered. Our secondary outcome was HRQL according to the SF-36.[23,24] HRQL was measured before,

and at three and twelve months after surgery. Change in HRQL was expressed by a delta score between the preoperative measurement and at one year after surgery, consisting of eight sub scores (i.e. physical functioning, role functioning, role emotional, social functioning, bodily pain, mental health, vitality and general health). Sub scores ranged from 0 to 100 and were summarized into a mental HRQL and physical HRQL score, with positive values representing improvement. Death was scored as 0 points.[16]

Statistical analysis

Data are presented as frequencies and percentages (%) for categorical data and as median with interquartile range (IQR) or mean with standard deviation (SD) for continuous data, as appropriate. Normal distribution of the variables was assessed with visual inspection of the histograms and Q-Q plots. Differences between patients with and without chronic pain one year after surgery were compared using the Chi square test for dichotomous or categorical variables or the Mann-Whitney U test or Student's T-test for continuous variables as appropriate. To investigate the association between each frailty domain and chronic pain one year after cardiac surgery, multivariable log-binomial regression analysis was performed to present effect estimates as risk ratios (RR) with accompanying 99% confidence interval (99% CI). To take multiple testing into account, we tested against a p-value of 0.01 and used a CI of 99%. Bonferroni adjustment was deemed inappropriate and too conservative as the different frailty domains are highly dependent on each other.[17] As chronic pain one year after cardiac surgery was relatively common, the rare disease assumption would not hold. This means that an odds ratio, would not approach the corresponding risk ratio, hampering the interpretation of our results for clinical practice.[25] All associations were adjusted for EuroSCORE II to take age, sex, comorbidities and weight of the procedure into account. Additionally, the association was adjusted for intraoperative use of remifentanil, preexisting chronic pain and use of internal mammary artery.[1,2,26–30] These confounders were a priori selected based on literature. Next, change of HRQL in all eight sub scores prior to and one year after surgery was compared between patients with and without chronic pain using a Wilcoxon signed-rank test, for this univariate analysis p-values ≤ 0.01 were considered statistical significant. To investigate the association of chronic pain with HRQL after one year, multivariable linear regression models were conducted, where physical and mental HRQL measured at 12 months were used as the outcome. All associations were adjusted for EuroSCORE II, preexisting chronic pain, overall frailty and physical or mental HRQL measured prior to surgery. Estimates are expressed as linear regression coefficients (β) with accompanying 99% CI. To assess the robustness of our findings, sensitivity analysis were performed using the same analytical approaches. The first post-hoc analysis excluded all patients who died within 12 months of follow up. In the second post-hoc analysis, only patients with new or worse pain one year after surgery

(i.e. reclassified into a higher grade of pain) were scored as chronic pain and patients with preexistent moderate to severe pain were excluded from this definition. As SF-36 data was missing for 11% of cases and could lead to potential bias, multiple imputation was conducted using the 'mice' library in R.[31,32] Twenty data sets were created and the estimates and variances for each of the imputed datasets were pooled into an overall estimate using Rubin's rule. The imputed dataset was used for final analyses. In order to obtain chronic pain categories after imputation, the mean frequencies of the specific answers to the SF-36 questionnaire at baseline and one year after surgery across the 20 imputation datasets were rounded to the nearest integer. An a priori sample size was not performed, as the sample size was based on the available data of the AGE study.[16] Data analysis was performed using R statistics (version 3.6.3, 2020).

RESULTS

Study population

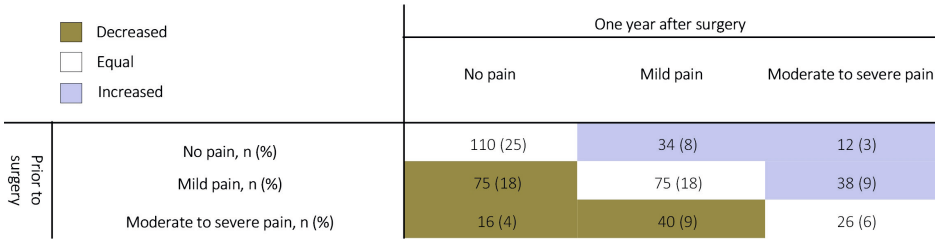
Overall, 518 patients were included in the analysis. Reasons for exclusion were withdrawal (n=9) or cancellation of surgery (n=17). Fifty-seven patients (11%) had one or more missing values (see additional **Supplementary table 2** for characteristics of patients with and without missing data). Prior to surgery, 91 patients (18%) were considered frail and chronic pain was reported by 331 patients (64%) of whom 77 (23%) were frail. Of all patients with preexisting chronic pain, 13% (44/331) used one analgesic and 7% (22/331) used two or more analgesics. Most common analgesics were acetaminophen (28/331, 9%), NSAIDs (18/331, 5%) and opioids (16/331, 5%). Patients with chronic pain prior to surgery more often used an antidepressant, 26/331 versus 4/187 (8% versus 2%), compared to patients without chronic pain prior to surgery (p=0.01). Additional, **Supplementary table 3** demonstrates the baseline characteristics for patients with and without chronic pain prior to surgery.

Frailty and chronic pain after cardiac surgery

140 patients (27%) reported improvement of pain, 243 (47%) had no or unchanged pain and 135 patients (26%) reported new or worse chronic pain one year after surgery (**Figure 1**). According to our definition, chronic pain was present in 182 patients (35%), which included 47 patients with pre-existent moderate to severe pain that was not improved. Baseline characteristics according to chronic pain after cardiac surgery are presented in **Table 1**. Patients with chronic pain had higher EuroSCORE II at baseline, more often used opioids and had lower test results in the physical frailty domains. Patients preoperatively considered frail had a higher risk of developing postoperative chronic pain (aRR 1.58, 99% CI 1.08 – 2.30). **Figure 2** demonstrates the association between each frailty domain and chronic pain one year after surgery. Medication use, living situation, mobility, gait speed, Nagi's physical functioning and preoperative HRQL were associated with chronic pain after surgery. Patients with preoperative excessive polypharmacy, patients who were living alone and patient with lower mental HRQL had increased risks to develop chronic pain (aRR 2.03, 99% CI 1.32 – 3.12, 1.54, 99% CI 1.11 – 2.13, and aRR 1.02 99% CI 1.01 – 1.03 per point decrease on mental HRQL, respectively). Also, preoperative impaired physical functioning was associated with postoperative chronic pain (aRR 1.11, 99% CI 1.04 – 1.18 per second increase on 5-MWT, aRR 1.06, 99% CI 1.02 – 1.10 per second increase on TGUG, aRR 1.32, 99% CI 1.19 – 1.46 per point increase on Nagi's scale and aRR 1.03, 99% CI 1.01 – 1.05 per point decrease on physical HRQL). When patients with preexistent moderate to severe pain were excluded from the chronic pain definition in the post-hoc analysis, mobility and preoperative HRQL were no longer significantly associated (see figure in

Supplementary figure 1). Exclusion of patients who died within 12 months of follow-up did not change the associations (see figure in **Supplementary figure 2**).

Figure 1. Pain intensity before and one year after surgery.



n: number.

Table 1. Baseline characteristics (n = 518).

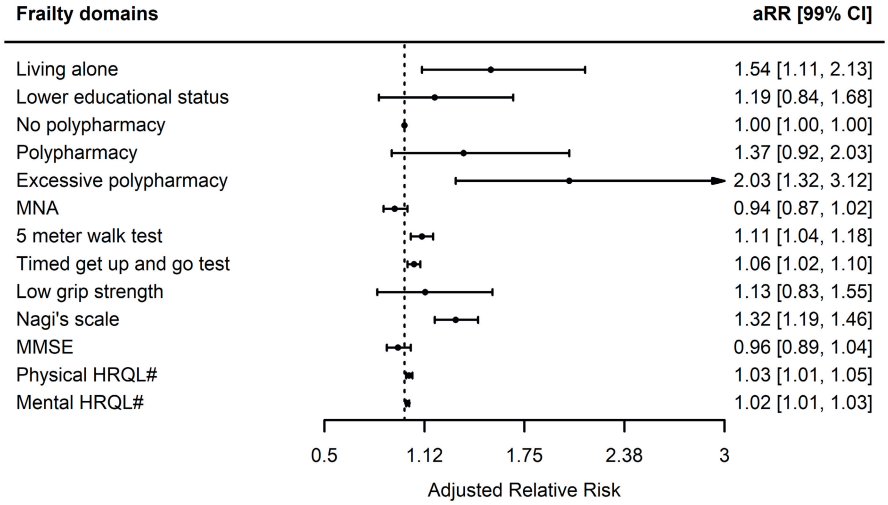
	No chronic pain (n = 336)	**Chronic pain** (n = 182)	**p-value**
Patient characteristics			
Male sex	240 (71)	109 (60)	0.01
Age, years	74 (72 – 77)	75 (72 – 78)	0.09
BMI ($kg \cdot m^{-2}$)	26.20 (24.20 – 28.70)	26.60 (24.42 – 30.10)	0.16
EuroSCORE II	1.69 (1.21 – 2.91)	2.16 (1.39 – 3.66)	0.001
Preoperative use of analgesics			
Acetaminophen	19 (6)	15 (8)	0.34
NSAIDs	12 (4)	11 (6)	0.28
Opioids	9 (3)	12 (7)	0.05
Antidepressants	14 (4)	16 (9)	0.05
Type of surgery			
Single CABG or maze	124 (37)	55 (30)	0.15
Single valve	91 (27)	53 (29)	0.70
Combined surgery	97 (29)	59 (32)	0.46
Aortic surgery	24 (7)	15 (8)	0.78
Duration of surgery, minutes	204 (163 – 250)	210 (168 – 258)	0.50
Remifentanyl (microgram)	2000 (1502 – 2000)	2000 (1079 – 2000)	0.004
Use of internal mammary artery	166 (49)	72 (40)	0.04
Length of stay in the ICU, days	1 (1 – 2)	1 (1 – 3)	0.04

Table 1. Baseline characteristics (n = 518). (continued)

	No chronic pain (n = 336)	**Chronic pain** (n = 182)	**p-value**
Length of hospital stay, days	8 (7 – 12)	9 (7 – 15)	0.07
Complication (re-thoracotomy)	15 (5)	13 (7)	0.28
Frailty domains			
Living alone	57 (18)	53 (29)	<0.01
Lower education	77 (23)	53 (29)	0.15
Polypharmacy	211 (63)	134 (74)	0.02
Excessive polypharmacy	42 (13)	46 (25)	<0.001
MMSE, points	29 (28 – 30)	29 (27 – 30)	0.37
5 Meter walk test, seconds	4.6 (4.1 – 5.3)	4.9 (4.2 – 5.9)	<0.001
Timed get up and go test, seconds	9.7 (8.5 – 11.2)	10.4 (8.7 – 12.8)	0.002
Low grip strength	118 (35)	71 (39)	0.45
Nagi's scale, points	0 (0 – 1)	1 (0 – 2)	<0.001
MNA, points	13 (12 – 14)	12.5 (11 – 14)	0.06
Mental HRQL, points	53.1 (44.1 – 58.0)	47.9 (37.7 – 54.0)	<0.001
Physical HRQL, points	44.6 (35.7 – 52.0)	41.0 (32.1 – 49.3)	0.005

Continuous values as mean (± standard deviation) or median (1st to 3rd quartile), categorical values as frequency (%). n: number; BMI: body mass index; NSAIDs: non-steroid anti-inflammatory drugs; CABG: coronary artery bypass grafting; ICU: intensive care unit; MMSE: minimal mental state examination; MNA: mini-nutritional assessment; HRQL: health related quality of life.

Figure 2. Adjusted relative risks for the development of chronic pain.

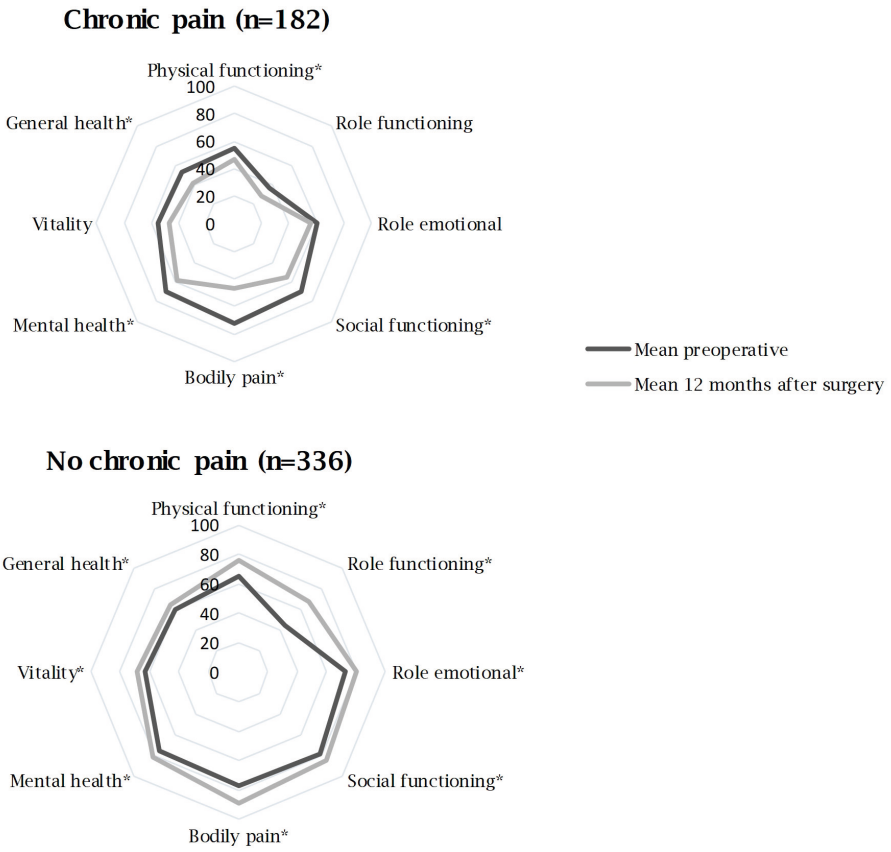


aRR: adjusted relative risk; CI: confidence interval; MMSE: minimal mental state examination; MNA: mini-nutritional assessment; HRQL: health related quality of life. Polypharmacy was added as factor with polypharmacy defined as ≥5 and <10 prescriptions and excessive polypharmacy defined as ≥10 prescriptions used. No polypharmacy was used as reference category. Log-binomial regression was used for statistical testing with correction for EuroSCORE II, intraoperative use of remifentanil, preexisting chronic pain and use of internal mammary artery. P-value ≤0.01 was considered statistically significant. #; per point decrease on physical and mental HRQL.

Chronic pain and quality of life at one year after surgery

Figure 3 demonstrates the mean change HRQL in all eight sub scores prior to and one year after surgery in patients with and without chronic pain. Patients without chronic pain significantly improved in each sub score, where patients with chronic pain worsened. Multivariable linear regression analysis demonstrated that patients with chronic pain reported worse physical HRQL one year after surgery compared to patients without chronic pain (β -10.37, 99% CI -12.57 – -8.17). Chronic pain was not associated with mental HRQL after one year (β -0.83, 99% CI – 3.26 – 1.60). Results were similar after excluding patients who were deceased within one year after surgery and also after the exclusion of patients with preexistent moderate to severe pain from the chronic pain definition.

Figure 3. Change in health related quality of life in eight sub-scores.



**p<0.01, tested with Wilcoxon signed-rank test.*

DISCUSSION

This study addressed the association between frailty domains and chronic pain following cardiac surgery in older patients. Additionally, the impact of chronic pain on HRQL in older patients was evaluated. One out of three elderly reported chronic pain after one year and frail patients had a higher risk of chronic pain following cardiac surgery. Frailty domains that were associated with chronic pain following surgery were medication use, living situation, mobility, gait speed, Nagi's physical functioning and preoperative HRQL. In addition, we found that postoperative chronic pain was associated with worse physical HRQL one year after surgery.

This study confirmed that chronic pain is common in elderly cardiac surgery patients with a similar incidence reported in prior studies.[1–3] However, in our study the number of patients with postoperative chronic pain (n=182) decreased compared to the number of patients with pain prior to surgery (n=331), and 27% of patients (140/518) reported an improvement in pain. This might be explained by an improved functional capacity, decreased ischemic chest pain and lower levels of anxiety following cardiac surgery. Nevertheless, increased pain symptoms were common. Considering that chronic pain had a profound effect on HRQL, identification of risk factors for development of chronic pain, especially in the frail and vulnerable population, is important and might help to initiate preventive strategies. Several risk factors including younger age, psychological impairment, preexisting pain, internal mammary artery harvest, use of remifentanil and emergency surgery have been described to increase the risk of chronic pain following cardiac surgery.[1,2,26–30] In contrast to prior studies, these risk factors were not associated with higher risks of the development of chronic pain in our study. This is likely explained by differences between surgical cohorts. The AGE study consisted of a frailty-prone population undergoing a wide range of elective cardiac surgery procedures, and the mean age was higher than in other reports.

Frail patients had a higher risk of developing postoperative chronic pain following cardiac surgery. This association might be explained by impaired physical exertion as higher levels of activity have been described to reduce pain sensitivity by decreased pain facilitation and increased pain inhibition.[33] Conversely, preexistent pain is well-known to have an impact on physical activity.[5,6] Furthermore, preexistent pain is known to be a risk factor for acute and chronic pain following surgery.[1,26,27] The question arises whether preexistent pain or impaired physical functioning (possibly due to pain or frailty) in these patients is the most relevant risk factor for the development of chronic pain. In our study, preexistent pain was not significantly associated with postoperative chronic pain. Also, in a post-hoc analysis, in which patients with preexistent moderate

to severe pain were excluded from the chronic pain definition, our results did not change. Consistent with prior research, this underlines the association between impaired physical functioning and the development of chronic postoperative pain.[33]

Besides impaired physical functioning, medication use, living situation and preoperative mental HRQL were associated with chronic postoperative pain. Polypharmacy is common in older patients, and might impede pain management for several reasons. Apart from age- and disease-related changes in physiology, disease-drug and drug-drug interactions might lead to a heterogeneity in response to medications and increased adverse drug effects. Frailty further increases this heterogeneity and thus frail elderly with polypharmacy may be more susceptible to adverse events.[11] Next to this, polypharmacy leads to medication non-adherence, leading to a suboptimal effect of prescribed analgesic therapy.[34] In our study, patients with excessive polypharmacy had a twofold risk to develop chronic pain. Finally, patients living alone are prone to social isolation, which contributes to feelings of depression or anxiety, and a more intense experience of pain.[11,26,35]

Gender has been described to interact with multiple preoperative factors as well as cardiac surgery outcomes.[36] Female gender has been positively associated with preoperative frailty, psychological disease and dementia in cardiac surgery patients.[36] The results of our study confirm the well-investigated relationship between female gender and chronic pain.[26,27] When defining interventions to improve outcome following cardiac surgery based on preoperative risk stratification, gender-related disparities should be taken into consideration.

Our study confirmed the existing relationship between chronic pain and HRQL. In general, polypharmacy, physical inactivity, reduced self-reliance and social isolation leads to an increase in health consumption, pain and poor HRQL.[11,27,28,37,38] In addition, several studies found that pain adversely affects recovery and HRQL, and that the impact correlated with the severity of pain.[27,28,37] In patients with chronic pain in our study, mental and physical HRQL were lower prior to surgery and physical HRQL was worse one year after surgery compared to patients without chronic pain ($p < 0.001$). Understanding factors that are related to HRQL in older people can be used to preoperatively accommodate patients' needs and preserve quality of life.

Risk stratification should lead to individualized evaluation and preparation for surgery. However, evidence for pre-habilitation is limited for cardiac surgery patients. However, preoperative exercise has been demonstrated to improve functional recovery.[39] Optimization of treatment expectations by a simple psychological intervention have

shown to improve disability.[40] Currently, trials on pre-habilitation are being performed in cardiac surgery patients, but the results have to be awaited.[41,42]

Comprehensive evaluation of pharmacotherapy should be part of each preoperative assessment, but deserves additional attention of, for example, a pharmacist or geriatrician in patients with polypharmacy. Patients suffering from chronic pain preoperatively should receive an individualized perioperative pain management plan, depending on their preoperative situation. Within this plan, additional pharmacotherapy, locoregional anesthesia and/or non-pharmacological interventions including may be considered to treat acute postoperative pain and prevent the increase of chronic pain symptoms following cardiac surgery.

The following limitations should be considered. First, pain was determined by a health survey that was not specifically designed to assess pain or pain interference. This study population reported pain within the last 4 weeks at 12 months follow up after surgery, and defined it as chronic pain.[43] Unfortunately, differentiation between thoracic pain, wound pain, chest pain, pain due to the surgical procedure or other pain, and type of pain (i.e., neuropathic, musculoskeletal, inflammatory, or mechanical pain) was not possible.[43] Second, a single point estimate was used for the incidence of chronic pain which may have resulted in an underestimation. Besides, the ageing process may account for differences in pain signaling and perception, causing an inconsistence and variety in pain measurements. More specific, with ageing a loss in structure and function of peripheral nerves occurs.[10,44] Due to a decrease in the spread and magnitude of brain activation in response to pain in elderly, pain thresholds might be higher.[10,44] On the other hand, endogenous pain modulation in elderly shows age-related impairment.[10,44] In particular, inhibitory systems were reported to be affected, resulting in lower capacities to modulate pain. This inadequacy to modulate pain leads to an increased risk for chronic pain. Finally, we did not register age-dependent conditions such as arthrosis and neurological conditions which may be related to frailty as well as to chronic pain. Further analysis of the reason for frailty may improve the prediction of chronic postoperative pain. Future research to explore these current findings should determine pain using patient diaries with validated pain assessments.

In conclusion, postsurgical chronic pain is common in elderly cardiac surgery patients. Preoperative polypharmacy, living alone, physical frailty, living alone and lower mental HRQL were positively associated to chronic pain following cardiac surgery. Secondly, chronic pain was associated with worse physical HRQL following cardiac surgery. The results of our study advocate that early identification of these factors may be used to identify older patients at risk for chronic pain after cardiac surgery.

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Supplementary table 1. Description of frailty domains.

Frailty domain	Test	Method of assessment	Cut off value
Nutritional status	Mini nutritional assessment	Six item questionnaire on weight loss, eating, BMI, and psychological status	A score ≤11 out of 14 identified patients at risk for malnutrition[17]
Gait speed	5-meter walk test	Patients were instructed to walk at their normal pace with walking aids if needed for five meters. Time between first footfall after the starting line and first footfall after the five meter line was recorded	Impaired gait speed was defined as ≥6 seconds or inability to perform the test[19]
	Timed get up and go test	Time was recorded between standing up from a seated position in a chair, walk for three meters with walking aids if needed and return to a seated position	Impaired gait speed was defined as ≥10 seconds or inability to perform the test[18]
Polypharmacy	Number of prescriptions	Assessment by hospital pharmacy services	≥5 and <10, ≥10 prescriptions (excessive)[40]
Daily functioning	Nagi's scale of physical disability	Seven item questionnaire on lifting heavy objects, kneeling, raising arms above the head, walking one flight of stairs, and walking 1.5 kilometers	A score ≥3 implied impairments[19]
Handgrip strength	Hydraulic handheld dynamometer	Best result of three consecutive tests to squeeze dynamometer with lower arm unsupported and in 90^{0} angle.	According to age and sex[20]
Cognition	Mini Mental State Examination	Eleven item questionnaire on orientation in time and place, short term memory, attention, and following verbal and written commands.	A score of ≤25 out of 30 was considered as mildly impaired cognition[21]
Health related quality of life	Medical Outcomes Study Short Form 36	36 item self-assessed questionnaire on physical and mental well-being generating two scores representing mental and physical health related quality of life	A deviation of >1 standard deviation from the population mean was considered impaired[22,23]
Living situation	Interview	Impaired when a patient was living without a partner or family	
Educational status	Interview	Impaired when no education beyond secondary education was followed	

BMI: body mass index.

Supplementary table 2. Baseline for patients with and without missing data.

	With missing data (n = 57)	Without missing data (n = 461)	P-value	Missing
Patient characteristics				
Male sex	41 (72)	308 (69)	0.53	0
Age, years	75 (73 – 77)	74 (72 – 77)	0.14	0
BMI ($kg \cdot m^{-2}$)	25.90 (24.60 – 28.70)	26.30 (24.20 – 29.10)	0.62	0
EuroSCORE II	2.33 (2.40 – 3.62)	1.80 (1.24 – 3.11)	0.03	0
Preoperative use of analgesics				0
Acetaminophen	3 (5)	31 (7)	0.89	
NSAIDs	3 (5)	20 (4)	1	
Opioids	2 (4)	19 (4)	1	
Antidepressants	2 (4)	28 (6)	0.63	
Type of surgery				0
Single CABG or maze	17 (30)	162 (35)	0.52	
Single valve	8 (14)	136 (30)	0.02	
Combined surgery	24 (42)	132 (28)	0.05	
Aortic surgery	8 (14)	31 (7)	0.09	
Duration of surgery, minutes	214 (178 – 318)	206 (162 – 250)	0.04	0
Remifentanyl (microgram)	1642 (1010 – 2000)	2000 (1458 – 2000)	0.001	17
Use of internal mammary artery	27 (47)	211 (46)	0.93	0

Supplementary table 2. Baseline for patients with and without missing data. (continued)

	With missing data (n = 57)	Without missing data (n = 461)	P-value	Missing
Length of stay in the ICU, days	2 (1 – 4)	1 (1 – 2)	0.001	0
Length of hospital stay, days	10 (7 – 19)	8 (7 – 13)	0.13	6
Complication (re-thoracotomy)	8 (14)	20 (4)	0.01	0
Frailty domains				
Living alone	16 (28)	94 (20)	0.24	0
Lower education	18 (32)	112 (24)	0.30	12
Polypharmacy	39 (68)	306 (66)	0.87	0
Excessive polypharmacy	12 (21)	76 (16)	0.50	0
MMSE, points	29 (27 - 30)	29 (28 - 30)	0.14	5
5 Meter walk test, seconds	4.8 (4.1 - 5.5)	4.7 (4.1 - 5.1)	0.61	6
Timed get up and go test, seconds	9.8 (8.5 - 12.0)	9.8 (8.6 - 11.6)	0.73	6
Low grip strength	24 (42)	165 (36)	0.44	1
Nagi's scale, points	0.0 (0.0 - 2.0)	0.0 (0.0 - 1.0)	0.66	2
MNA, points	13 (11 - 14)	13 (12 - 14)	0.51	0
Mental HRQL, points	52.4 (41.6 - 56.1)	51.6 (42.1 - 57.4)	0.76	7
Physical HRQL, points	45.2 (37.0 - 52.2)	42.6 (33.7 - 51.0)	0.12	7

Continuous values as mean (± standard deviation) or median (1st to 3rd quartile), categorical values as frequency (%). n: number; BMI: body mass index; NSAIDs: non-steroid anti-inflammatory drugs; CABG: coronary artery bypass grafting; ICU: intensive care unit; MMSE: minimal mental state examination; MNA: mini-nutritional assessment; HRQL: health related quality of life.

Supplementary table 3. Baseline for patients with and without chronic pain prior to surgery (n = 518).

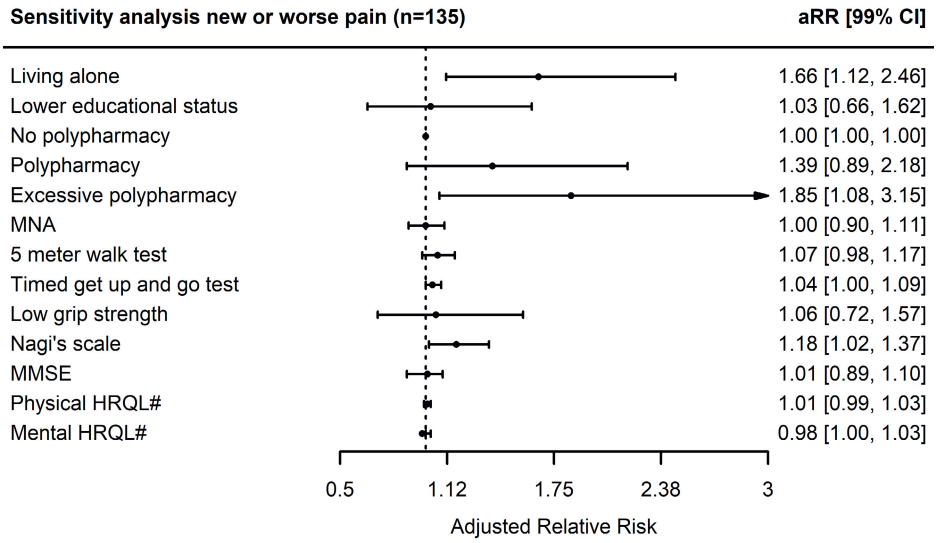
	No chronic pain prior to surgery (n = 187)	**Chronic pain prior to surgery** (n = 331)	**p-value**
Patient characteristics			
Male sex	135 (72)	214 (65)	0.10
Age, years	74 (72 – 77)	75 (72 – 77)	0.85
BMI ($kg \cdot m^{-2}$)	25.80 (23.75 – 27.90)	26.90 (24.50 – 29.75)	0.001
EuroSCORE II	1.88 (1.22 – 3.21)	1.81 (1.25 – 3.28)	0.92
Preoperative use of analgesics			
Acetaminophen	6 (3)	28 (9)	0.03
NSAIDs	6 (3)	17 (5)	0.42
Opioids	5 (3)	16 (5)	0.33
Antidepressants	4 (2)	26 (8)	0.01
Type of surgery			
Single CABG	45 (24)	134 (41)	< 0.001
Single valve	60 (32)	84 (25)	0.13
Combined surgery	63 (34)	93 (28)	0.22
Aortic surgery	19 (10)	20 (6)	0.13
Duration of surgery, minutes	212 (160.5 – 262.5)	205 (166.5 – 249)	0.35
Remifentanyl (microgram)	2000 (1254.50 – 2000)	2000 (1420 – 2000)	0.16
Use of internal mammary artery	75 (40)	163 (49)	0.06
Length of stay in the ICU, days	1 1 – 2.5)	1 (1 – 2)	0.19
Length of hospital stay, days	9 (7 – 13)	9 (7 – 13)	0.91
Complication (re-thoracotomy)	8 (4)	20 (6)	0.52
Frailty domains			
Living alone	30 (16)	80 (21)	0.04
Lower education	39 (21)	91 (27)	0.12
Polypharmacy	103 (55)	242 (73)	< 0.001
Excessive polypharmacy	22 (12)	66 (20)	0.02
MMSE, points	29 (28 - 30)	29 (27 - 30)	0.15
5 Meter walk test, seconds	4.5 (4.0 - 5.1)	4.8 (4.2 - 5.7)	< 0.001
Timed get up and go test, seconds	9.5 (8.3 - 11)	10.1 (8.7 - 12.1)	< 0.001

Supplementary table 3. Baseline for patients with and without chronic pain prior to surgery (n = 518). (continued)

	No chronic pain prior to surgery (n = 187)	Chronic pain prior to surgery (n = 331)	p-value
Low grip strength	61 (33)	128 (39)	0.19
Nagi's scale, points	0 (0 - 1)	1 (0 - 2)	< 0.001
MNA, points	13 (12 - 14)	13 (12 - 14)	0.16
Mental HRQL, points	53.1 (44.0 - 57.6)	51.3 (40.3 - 57.0)	0.16
Physical HRQL, points	51.3 (45.2 - 54.8)	37.6 (30.5 - 45.7)	< 0.001

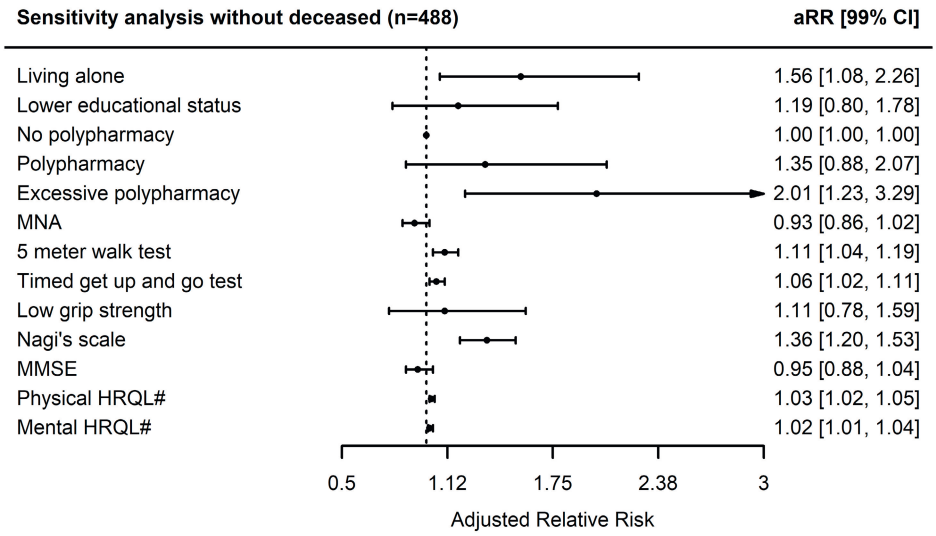
Continuous values as mean (± standard deviation) or median (1st to 3rd quartile), categorical values as frequency (%). n: number; BMI: body mass index; NSAIDs: non-steroid anti-inflammatory drugs; CABG: coronary artery bypass grafting; ICU: intensive care unit; MMSE: minimal mental state examination; MNA: mini-nutritional assessment; HRQL: health related quality of life.

Supplementary figure 1. Adjusted relative risks for the development of new or worse chronic pain, sensitivity analysis (n = 135).



aRR: adjusted relative risk; CI: confidence interval; MMSE: minimal mental state examination; MNA: mini-nutritional assessment; HRQL: health related quality of life. Polypharmacy was added as factor with polypharmacy defined as ≥5 and <10 prescriptions and excessive polypharmacy defined as ≥10 prescriptions used. No polypharmacy was used as reference category. Log-binomial regression was used for statistical testing with correction for EuroSCORE II, intraoperative use of remifentanil, preexisting chronic pain and use of internal mammary artery. P-value ≤0.01 was considered statistically significant. #; per point decrease on physical and mental HRQL.

Supplementary figure 2. Adjusted relative risks for the development of chronic pain, sensitivity analysis without deceased patients (n = 488).



aRR: adjusted relative risk; CI: confidence interval; MMSE: minimal mental state examination; MNA: mini-nutritional assessment; HRQL: health related quality of life. Polypharmacy was added as factor with polypharmacy defined as ≥5 and <10 prescriptions and excessive polypharmacy defined as ≥10 prescriptions used. No polypharmacy was used as reference category. Log-binomial regression was used for statistical testing with correction for EuroSCORE II, intraoperative use of remifentanil, preexisting chronic pain and use of internal mammary artery. P-value ≤0.01 was considered statistically significant. #; per point decrease on physical and mental HRQL.

Chapter 4

Continuous monitoring of vital signs and clinical deterioration in frail elderly cardiac surgery patients, AGE AWARE study:

A prospective observational cohort study.

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ABSTRACT

Introduction

Frail patients are at increased risk for postoperative complications. Continuous monitoring of vital signs can detect clinical deterioration early. This study analyses continuous vital signs before clinical deterioration in frail cardiac surgery patients at the general ward.

Methods

A prospective, single center study in frail patients undergoing cardiac surgery. Primary endpoint was clinical deterioration, defined as modified Early Warning Score (MEWS) ≥ 5. Heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO_2) were continuously monitored for 72 hours at the general ward. Predefined thresholds were used to define abnormal HR, RR and SpO_2 during 4 hours before clinical deterioration and compared with controls. Duration in minutes and time weighted average (TWA) of abnormal vital signs were calculated to examine the association with clinical deterioration using logistic regression analysis.

Results

Clinical deterioration occurred in 22/70 (31%) patients. RR was abnormal during 70% of the time, but not different between groups (71% vs. 68%, P=0.60). TWA of abnormal RR was associated with clinical deterioration (OR 2.54, 95% CI 1.05 – 6.47). Among patients with clinical deterioration, oxygen use >5L O_2/min and arrhythmia were more common (77% vs. 54% among controls, P<0.001 and 31% vs. 11% of controls, P<0.01, respectively). However, abnormal continuous SpO_2 and HR measurements were not associated with clinical deterioration.

Conclusion

Frail patients often experience postoperative clinical deterioration at the general ward. Clinical deterioration was preceded by more severe abnormal RR compared to controls, but not by differences in abnormal HR or SpO_2.

INTRODUCTION

Population aging and healthcare innovations have increased the number of elderly undergoing cardiac surgery. Cardiac surgery aims to improve functional capacity and overall survival in elderly patients, but may also precipitate major morbidity and mortality.[1-3] Perioperative management of older patients is complex due to multiple comorbidities and frailty. As a result, a significant number of elderly experience a complication after surgery.[4,5] Especially frail patients are at increased risk for complications, leading to longer length of stay, in-hospital mortality and poor functional recovery.[4,6-9] The majority of complications occur on the general ward during the early postoperative period, with limited monitoring of vital signs.[1-3,8,10,11]

Complications are often preceded by minutes to hours of vital sign deterioration.[2,3,12] Modified early warning scores (MEWS) are used by nurses to quickly asses clinical status using vital signs, including heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO_2).[13] MEWS are used to activate rapid response teams if clinical deterioration is detected.[14-18] Timely intervention of complications is crucial, as delayed treatment is associated with increased morbidity and mortality.[14,19] As MEWS are typically recorded once every 8 hours, early signs of deterioration could easily be missed.

Continuous monitoring of vital signs in surgical patients at the general ward may have the potential to early detect clinical deterioration and improve outcomes.[20-25] In recent years, wireless devices capable of continuously monitoring of vital signs have become available.[26,27] This study analyses vital signs, according to predefined thresholds for HR, RR and SpO_2, using continuous monitoring in frail elderly prior to clinical deterioration following cardiac surgery. The central hypothesis is that clinical deterioration is preceded by significant changes in vital signs.

METHODS

Ethics

Ethical approval for this study (Medical Ethics Research Committee United, number R19.018) was provided by the local ethics committee of St. Antonius Hospital, Nieuwegein, the Netherlands (Chairperson Dr. R.J.E. Grouls) on 12 September 2019.

Design

The Anaesthesia Geriatric Evaluation (AGE) AWARE study was a single centre prospective observational cohort study in the Netherlands (St. Antonius Hospital, Nieuwegein). Inclusion took place from March 2020 until December 2021. The study was registered at clinicaltrials.gov (identifier: NCT03944967) and performed in accordance with the Declaration of Helsinki. All patients provided written informed consent. This manuscript adheres to the applicable STROBE guidelines.[28]

Population and setting

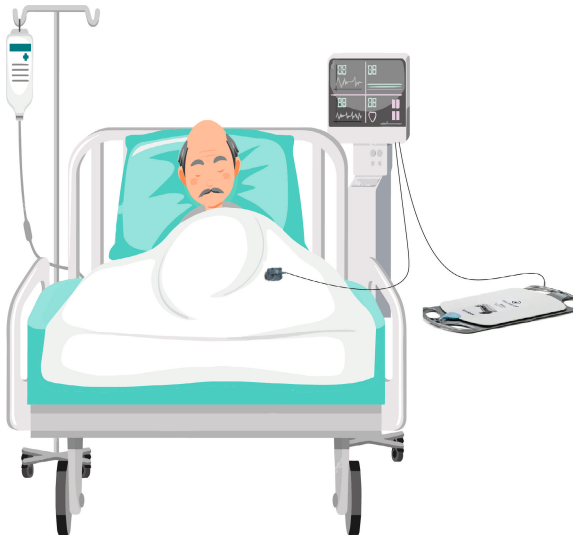
This study included patients aged ≥ 70 years with clinical frailty scale (CFS)[29] ≥ 4, undergoing elective open cardiac surgery. All patients visited the outpatient anaesthesia clinic for routine preoperative screening. According to local procedures patients were postoperatively admitted to the intensive care unit (ICU) for at least one day, depending on surgical risk. A patient was transferred to the general ward for further recovery after meeting protocolled ICU discharge criteria. These criteria included; complete recovery from anaesthesia, hemodynamically stability with no evidence of significant bleeding, core body temperature >36 °C and normal blood gas values. At arrival on the general ward, patients were connected to the continuous monitoring device.

Vital sign monitoring

Postoperative vital signs were monitored using the EarlySense system (EarlySense Ltd, Ramat Gan, Israel). The EarlySense is indicated for the remote continuous non-invasive monitoring of HR, RR and SpO_2 in hospitalised patients and consists of a contactless piezoelectric sensor that is placed under the mattress, a bedside monitor and re-usable oximeter. An overview of the measurement setup is demonstrated in **Figure 1**. The sensor and oximeter measures HR, RR and SpO_2 six times a minute. Both sensors are connected to the monitor that averages and displays the measurements every 60 seconds, as long as the patient remains in bed for HR and RR, and as long as the patient is connected to the oximeter for SpO_2. In cases of signal instability for HR and RR, characterised by excessive talking, eating, prolonged patient movement, or irregular HR or RR patterns such as periodic breathing or arrhythmia, the system defaults and the signal freezes. When a proper signal is being detected, the measurement resumes.

Patients were continuously monitored for three consecutive postoperative days (i.e. 72 hours) or until hospital discharge, death or readmission to the ICU. For this study, continuously measured data were blinded for patients and healthcare professionals.

Figure 1. Overview of measurement setup with the EarlySense remote monitoring system.



Routine spot check MEWS measurements were conducted by nurses at least every 8 hours at the general ward or more frequently on clinical indication. **Table 1** shows the predefined EWS thresholds for the MEWS scoring system. According to local protocols, appropriate measures were taken when MEWS increased, varying from increasing the spot check frequency to activating the rapid response team.

Missings and artefacts

Artefacts of continuous monitoring data were labelled as missing in case vital signs were outside physiological ranges; HR: 20 – 200 bpm, RR: 3 – 50 breaths/min and SpO_2: 60 – 100%. If patients had missing values <5 minutes, we applied the last measured value carried forward. If a period of missing values lasted ≥ 5 minutes and <10 minutes, we used the calculated average of the last measured values at the beginning and end of this period and altered the missing values into this average. If a period of missing values exceeded 10 minutes, all values were coded as missing. Finally, the data were classified according to the predefined EWS thresholds following the MEWS scoring system (**Table 1**). For example, a HR of 120 bpm was assigned an EWS HR 2, and a RR of 25 breaths/min an EWS RR 2. Henceforth, we will refer to the predefined EWS thresholds for each vital sign as EWS HR, EWS RR and EWS SpO_2.

Table 1. (M)EWS scoring system.

(M)EWS	3	2	1	0	1	2	3
RR/min		<9		9 – 14	15 – 20	21 – 30	>30
HR/min		<40	40 – 50	51 – 100	101 – 110	111 – 130	>130
SBP (mmHg)	<70	70 – 80	81 – 100	101 – 180	181 – 200	201 – 220	>220
Oxygen administration					<5L O_2/min	≥5L O_2/min	
SpO_2 (%)	<85	85 – 89	90 – 95	>95			
Temperature (°C)		<35	35.0 – 36.0	36.1 – 37.3	37.4 – 38.5	>38.5	
AVPU			Agitated	Alert	Verbal	Pain	Unresponsive
Urine production	Decreased last 6 hours: 1 point			Normal	Excessive last 6 hours: 1 point		
'Sense of unease' nurse: 1 point							

(M)EWS: (modified) early warning score system; RR: respiratory rate; HR: heart rate; SBP: systolic blood pressure; SpO_2: oxygen saturation; AVPU: alert, verbal, pain unresponsive.

For spot check MEWS measurements conducted by nurses, the following assumptions were made: in case of a missing value for oxygen administration, we assumed no additional oxygen administration; In case urine production was missing, we assumed urine production was 'Normal'; If 'sense of unease' nurse was missing, we assumed there was 'None'; and, if Alert, Verbal, Pain, Unresponsive (AVPU) was missing, we assumed the patient was 'Alert'. These assumptions were made based on our expectation that a deviating value would have been clearly documented by nurses.

Primary outcome

The primary endpoint was clinical deterioration within 72 hours after ICU discharge. Clinical deterioration was defined as MEWS ≥ 5 using spot check EWS monitoring by nurses.[17,18] The analysis was performed based on the first occurrence of clinical deterioration in each patient.

Selection of continuously measured vital sign data

Continuous vital sign data were analysed during the 4 hours before clinical deterioration. For each patient with clinical deterioration a control group was established, including multiple patients without clinical deterioration with data recorded over the same 4 hour time period. For example, in a patient experiencing clinical deterioration at 12 hours after arrival at the general ward, the data from 8 – 12 hours was analysed and compared with continuous data in the same period of controls. By conducting comparisons at corresponding time points, a fair assessment was achieved between patients with clinical deterioration and controls, accounting for their stages in the postoperative recovery process.

Sample size analysis

Few data is available on vital sign deteriorating after ICU discharge in cardiac surgery patients. Patients may experience frequent, short episodes of severe deteriorated vital signs; or vital signs may linger slightly below potentially harmful thresholds for hours. For this reason we choose predefined threshold values to define a deterioration of HR, RR and SpO_2. This makes it difficult to perform a formal sample size calculation. Our pilot study enrolled 70 patients, based on practical feasibility and in accordance with other studies on postoperative remote monitoring of vital signs.[21,32,33] With 70 patients and an incidence of deterioration >30%, we are confident to be able to test the hypotheses. It should be noted that the sample size deviates from the originally registered in the protocol at clinicaltrials.gov, as a result of prolonged slow patient enrolment due to a declining operating room program.

Statistical analysis

Baseline characteristics of patients with clinical deterioration were compared to controls. Descriptives were presented as frequencies and percentages (%) for dichotomous and categorical data and for continuous data as mean ± SD. Although data was not normally distributed, mean values were reported for clinically implications. Differences were tested using the independent T-test for continuous variables or a chi-square or Fisher's exact test for categorical variables, as appropriate.

For the spot check EWS monitoring performed by nurses over the complete 72 hour period, the proportion of measurements within each EWS threshold was calculated and compared between patients with clinical deterioration and controls. For each of the continuously measured vital signs, the duration and severity of abnormal vital signs was calculated for patients with clinical deterioration and controls during the selected 4 hour period. Duration was computed as the mean number of minutes spent within each EWS threshold. Severity of vital sign abnormality was expressed as the time weighted average (TWA). The TWA was constructed by calculating the area under the threshold (AUT) divided by the total measured monitoring time. An example of the TWA calculation is presented in **Supplementary figure 1.**

For each vital sign, the association between the duration of abnormal vital signs and TWA with clinical deterioration was analysed using logistic regression models. Effect estimates are expressed as ORs with corresponding 95% CI. P-values of ≤ 0.05 were considered statistically significant. Data analysis was performed using R statistics (version 1.4.1717, 2009-2021 Rstudio).

RESULTS

The AGE AWARE study included 95 patients. In 4 patients (4%) surgical treatment was changed and no longer met the inclusion criteria; 4 patients (4%) died before ICU discharge and 2 patients (2%) had a postoperative complication before continuous monitoring. Furthermore, 15 patients (16%) were not monitored due to a limited number of monitoring systems. In total, 70 patients were included in the analysis, with a median monitoring time of 72 hours [IQR 52 – 72]. Reasons for early discontinuation of monitoring included: transfer to another hospital for further recovery (12/24 patients, 50%), technical problems with the monitoring system (9/24 patients, 38%), readmission to the ICU (2/24 patients, 8%) or full recovery and discharge to home (1/24 patients, 4%). Baseline characteristics were not different between patients with clinical deterioration and controls (**Table 2**). A median of 11 spot check MEWS measurements were conducted per patient during the first 72 hours [IQR 9 – 13] (**Supplementary table 1**). Clinical deterioration was observed in 22 (31%) patients. The median time until the occurrence of clinical deterioration was 31 hours [IQR 14 – 42 hours] after arrival at the general ward. A total of 18 patients with clinical deterioration were included in the analysis, as 4 patients did not have 4 hours of continuous monitoring data prior to the occurrence of clinical deterioration. Overall 16% of continuous HR, 17% of continuous RR and 54% of continuous SpO_2 data, in the 4 hours prior to clinical deterioration was missing.

Table 2. Baseline characteristics.

Patient characteristics	Clinical deterioration	Control	P-value
Sex, male/female sex	14/4 (78%/22%)	35/17 (67%/33%)	0.59
Age, yrs	76 (74 – 77)	75 (74 – 78)	0.84
EuroSCORE II	1.9 (1.5 – 2.9)	1.8 (1.3 – 3.0)	0.46
Clinical Frailty Scale			0.23
4	9 (50%)	30 (58%)	
5	9 (50%)	17 (33%)	
6 or more	0	5 (9%)	
Total *n* of medication	7 (5 – 8)	7 (6 – 8)	0.42
Type of surgery			
Single CABG	5 (28%)	21 (40%)	0.50
Single valve	8 (44%)	13 (25%)	0.21
Aortic surgery	0	3 (6%)	0.71
Combined surgery	5 (28%)	15 (29%)	1

Table 2. Baseline characteristics. (continued)

Patient characteristics	Clinical deterioration	Control	P-value
Length of stay ICU, days	1 (1 – 1)	1 (1 – 1)	0.27
Readmission ICU	4 (22%)	1 (2%)	0.02
Length of hospital stay, days	9 (7 – 16)	7 (6 – 9)	0.02

Continuous variables reported as median (IQR), categorical variables as frequency (%).
N/no.: number; yrs: years; CABG: coronary artery bypass grafting; ICU: intensive care unit.

Continuous vital sign monitoring

Table 3 demonstrates the mean duration in minutes spent within each EWS thresholds for HR, RR and SpO_2 during the 4 hour period. Continuous HR monitoring revealed that EWS HR 0, indicative of a normal HR, was observed during 73% of the time in patients with clinical deterioration, compared to 80% of the time in the control group (P=0.377). Nevertheless, MEWS spot checks revealed an irregular HR in 31% of patients with clinical deterioration, compared to 11% in controls (P<0.01). This can be explained by the inability of the EarlySense system to capture irregular HR. Duration of abnormal HR was not associated with increased risks of clinical deterioration (**Supplementary table 2**). Additionally, TWA for HR was not significantly different between groups and not associated with clinical deterioration (OR 5.19, 95% CI 0.82 – 21.42, **Table 4**).

An abnormal RR (EWS RR >0) was very common in frail patients after cardiac surgery. In the 4 hours before clinical deterioration, EWS RR >0 occurred during 70% of the time, which was not different for patients with clinical deterioration and controls (P=0.60). No association was found between duration of abnormal RR and clinical deterioration (**Table 3 and Supplementary table 2**). TWA for RR was 1.43 for patients with clinical deterioration and 1.17 in controls (P=0.09). Severity of abnormal RR was associated with an increased odds for clinical deterioration (OR 2.54, 95% CI 1.05 – 6.47). This implies, for example, that patients with a mean EWS RR 2 over the complete measuring period exhibit a 2.54-fold increased odds of developing clinical deterioration compared to patients with a mean EWS RR 1 (P=0.04).

Hypoxemia requiring O_2 therapy after cardiac surgery was common (**Supplementary table 1**). Specifically, 77% of the MEWS spot check measurements indicated oxygen use >5L O_2, in patients with clinical deterioration compared to 54% among controls (P<0.001). Duration of EWS SpO_2 ≥ 2 was longer in the control group (27 minutes vs. 13 minutes in patients with clinical deterioration, P=0.02). The association between the duration of EWS SpO_2 2 and clinical deterioration was negative (OR 0.92, 95% CI

0.85 – 0.98, **Supplementary table 2**). This may be explained by higher amounts of O_2 therapy after cardiac surgery among patients experiencing deterioration, masking desaturation (**Supplementary table 1**). TWA of hypoxemia was not different between groups and not associated with clinical deterioration (OR 0.67, 95% CI 0.31 – 1.32), **Table 4**).

Table 3. Duration spent within each EWS threshold during the 4-hour period.

	Clinical deterioration	Control	P-value
Heartrate EWS 0	175 ± 76	195 ± 58	0.377
Heartrate EWS 1	18 ± 47	10 ± 35	0.49
Heartrate EWS 2	2 ± 4	1 ± 6	0.361
Heartrate EWS 3	1 ± 3	0 ± 0	0.347
Heartrate missing	*43 ± 50*	*32 ± 47*	*0.545*
Respiratory rate EWS 0	25 ± 53	36 ± 59	0.472
Respiratory rate EWS 1	77 ± 74	101 ± 68	0.228
Respiratory rate EWS 2	82 ± 69	60 ± 67	0.187
Respiratory rate EWS 3	13 ± 24	3 ± 10	0.126
Respiratory rate missing	*42 ± 49*	*38 ± 48*	*0.922*
Oxygen saturation EWS 0	22 ± 45	25 ± 52	0.807
Oxygen saturation EWS 1	52 ± 66	79 ± 86	0.15
Oxygen saturation EWS 2	10 ± 15	20 ± 41	0.022
Oxygen saturation EWS 3	3 ± 12	7 ± 25	0.243
Oxygen saturation missing	*151 ± 88*	*108 ± 102*	*0.079*

Mean number of minutes per EWS threshold during 4 hour period with standard deviation. Data is not normally distributed, so an independent t-test is performed. We reported the mean for clinically implications.

Table 4. Severity of abnormal vital signs during the selected 4-hour period.

	Clinical deterioration	Control	P-value
TWA HR	0.15	0.06	0.19
TWA RR	1.43	1.17	0.09
TWA SpO_2	0.64	0.83	0.24

TWA: time weighted average; HR: heart rate; RR: respiratory rate; SpO_2: oxygen saturation.

DISCUSSION

This study demonstrates that clinical deterioration is common after cardiac surgery, with an incidence of 31% in frail elderly patients at the general ward. In the 4 hours prior to clinical deterioration, there were no differences in vital signs between patients with clinical deterioration and controls. However, continuous monitoring of RR might be able to early detect deteriorating patients, as TWA of abnormal RR was significant associated with higher odds of clinical deterioration.

Patients admitted to hospitals nowadays often present with increasingly complex health problems and a higher chance of experiencing severe illness during hospital stay.[34] It is known that a delayed or absent response to deterioration has been labelled as 'failure to rescue', leading to escalation of care.[12,15–17,25] In addition, calculating trends over time and vital sign variability have been proved to be independent predictors of critical illness in ward patients.[12,23–25] Henceforth, it is more important than ever that health care personnel on the general ward can identify early signs of clinical deterioration. As nurses measure vital signs once every 8 hours, early identification of deterioration might easily be missed.[14–17] Today, a lot of effort is going into developing continuous monitoring systems capable of identifying changes in patients' medical condition that could result in deterioration.[12,14,15,17,25] Few studies on combined surgical and medical wards found early identification of deterioration, increased rapid response activation and a decreased need for patient rescue as benefits of continuous monitoring.[10,12,35] In the nonsurgical population, implementation of continuous monitoring was associated with a significant decrease in mortality.[36] Nevertheless, research in the surgical population is limited. As far as we know, no research has been conducted in the frail elderly population undergoing cardiac surgery, which presents a compounded level of risk. In frail elderly following cardiac surgery in our study, RR was abnormal for the majority of time. Additionally, we found an association between severity of abnormal RR and higher odds of clinical deterioration. This association did not demonstrate clinical differences in our population because the variance in TWA between the groups was small. Yet, this might be attributable due to early identification and treatment of patients with abnormal RR by nurses using MEWS measurements, potentially masking the differences observed with continuous monitoring, resulting in a small TWA difference between both groups. Efforts to implement continuous monitoring assume it will provide clinically valuable trends superior than measuring vital signs with fixed thresholds by intermittent monitoring. Different studies found RR to be the most accurate predictor in detecting clinical deterioration.[23–25] They specifically referred to the analysis of trends in vital signs, such as variability in RR and minimum SpO_2.[23–25] As RR was abnormal 70% of the time of MEWS measurements

in all frail elderly patients and TWA for abnormal RR was significantly associated with clinical deterioration, this might provide treatment options to improve patient outcome after cardiac surgery.

Our study has limitations. Most importantly, due to the nature of the monitoring system, HR and RR were recorded exclusively when the patient was in bed, while SpO_2 was measured only when the device was attached to the patients' finger. Instances when patients were out of bed due to required transportation for examinations or when patients were ambulatory due to recovery, contributed to a significant amount of missing data and might have led to attrition bias. The potential attrition bias is likely because of patients who were doing well discontinued continuous monitoring. Furthermore, the monitoring device was unable to capture irregular heart rhythms, which are frequently observed among post cardiac surgery patients. As a result, continuous HR monitoring in our study proved inadequate for early detection of clinical deterioration. Lastly, as our sample size was relatively small and the analysis was performed in a high risk population, the generalizability is limited.

Conclusions

In conclusion, frail elderly patients often experience clinical deterioration at the general ward following cardiac surgery. Clinical deterioration was preceded by more severe abnormal RR compared to controls, but not by differences in abnormal HR or SpO_2. Before implementation of continuous noninvasive ward monitoring, we need to await the results of adequately powered randomised controlled trials demonstrating its effectiveness in preventing clinical deterioration to improve surgical patient outcome.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Proportion of scored EWS thresholds by MEWS spot check measurements over the complete 72 hour measurement period.

MEWS	Clinical deterioration	Control	P-value
Heartrate EWS 0	82%	96%	0.096
Heartrate EWS 1	3%	3%	0.56
Heartrate EWS 2	5%	1%	<0.01
Heartrate EWS 3	10%	0	0.05
Respiratory rate EWS 0	6%	32%	<0.001
Respiratory rate EWS 1	69%	65%	<0.001
Respiratory rate EWS 2	21%	3%	<0.001
Respiratory rate EWS 3	3%	0	<0.001
SpO_2 EWS 0	82%	83%	0.052
SpO_2 EWS 1	17%	17%	0.294
SpO_2 EWS 2	<1%	<1%	0.257
SpO_2 EWS 3	<1%	0	0.331
Oxygen administration EWS 0	23%	46%	0.166
Oxygen administration EWS 1	67%	51%	0.009
Oxygen administration EWS 2	10%	3%	0.124
Systolic bloodpressure EWS 0	85%	91%	0.102
Systolic bloodpressure EWS 1	13%	9%	0.178
Systolic bloodpressure EWS 2	1%	0	0.331
Systolic bloodpressure EWS 3	<1%	0	0.331
Temperature EWS 0	55%	46%	0.042
Temperature EWS 1	44%	53%	0.50
Temperature EWS 2	1%	1%	0.596
Urine production EWS 0	99%	100%	0.017
Urine production EWS 1	<1%	0	0.331
Urine production EWS 2	<1%	0	0.331
“Sense of unease” nurse	2%	0	0.163
Abnormal AVPU	0	0	-

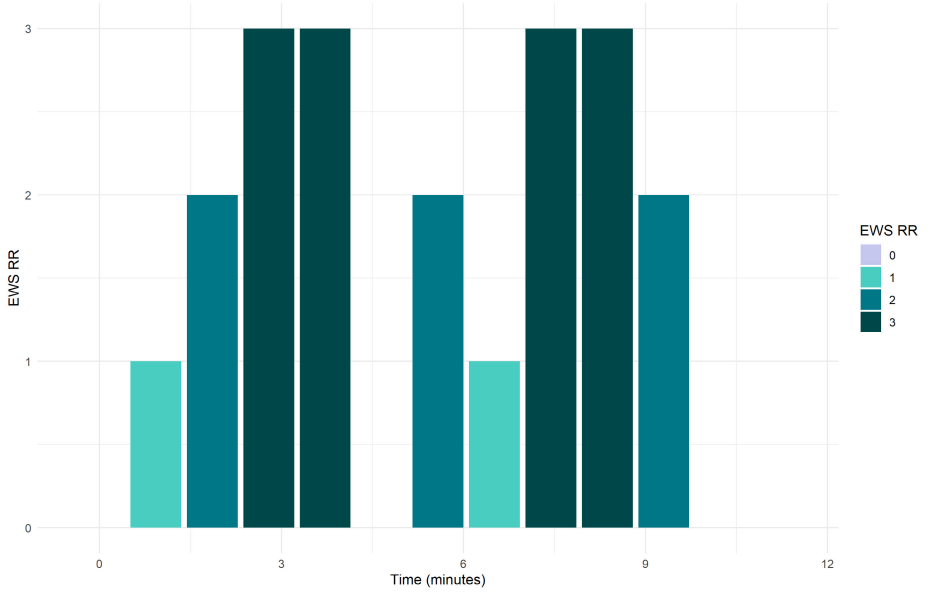
Categorical variables as frequency (%); % of spot check measurements in each category; (M) EWS: (modified) early warning score system; SpO_2: oxygen saturation; AVPU: alert, verbal, pain unresponsive.

Supplementary table 2. Association between duration in minutes within each EWS threshold and clinical deterioration.

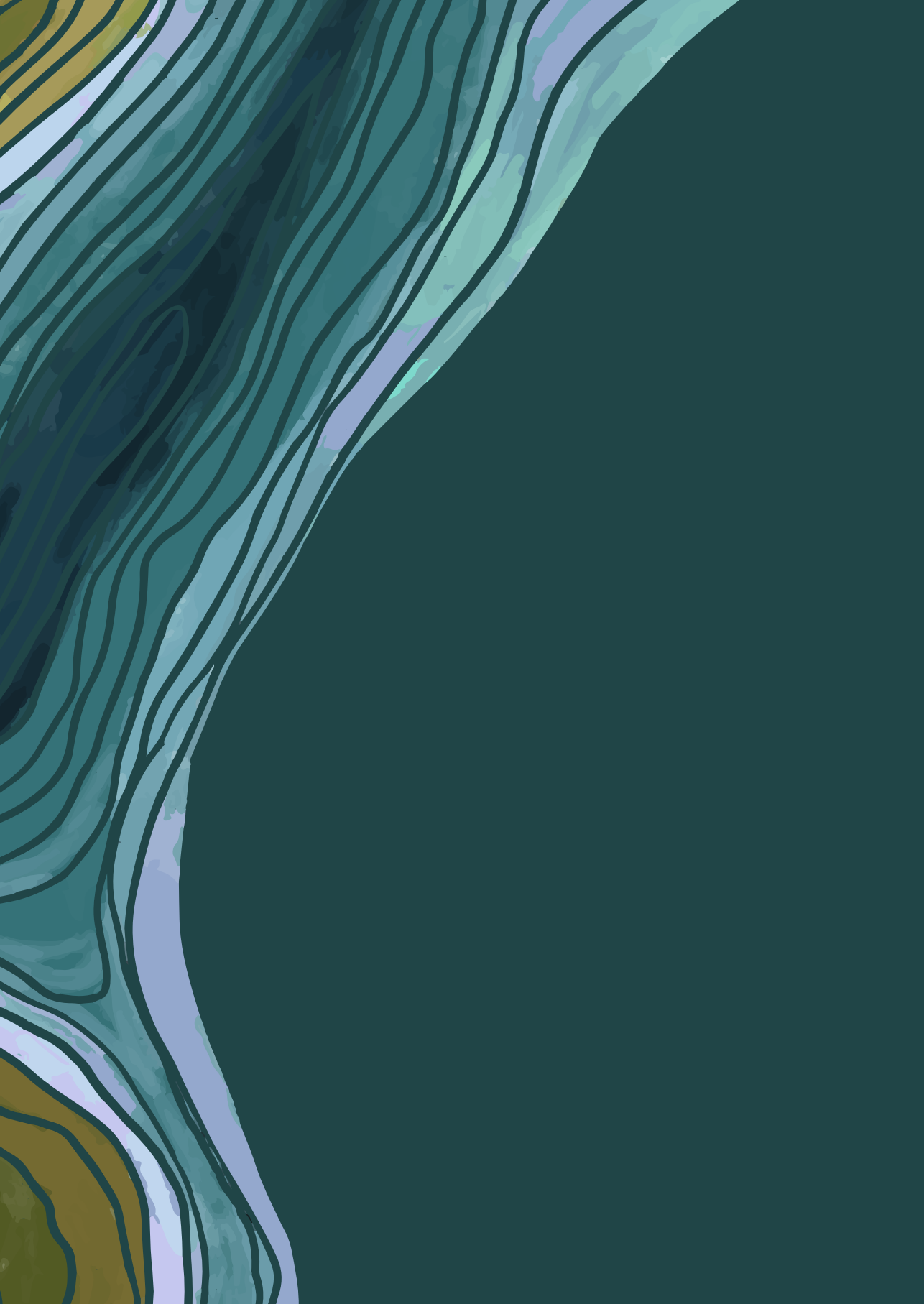
	Odds Ratio	95% CI	P-value
Heartrate EWS 0	0.99	0.98 – 1.01	0.37
Heartrate EWS 1	1.01	0.99 – 1.05	0.50
Heartrate EWS 2	1.14	0.88 – 1.69	0.37
Heartrate EWS 3	1.41	0.84 – NA*	0.60
Respiratory rate EWS 0	0.99	0.97 – 1.01	0.47
Respiratory rate EWS 1	0.99	0.98 – 1.00	0.22
Respiratory rate EWS 2	1.01	1.00 – 1.02	0.18
Respiratory rate EWS 3	1.07	1.00 – 1.22	0.18
Oxygen saturation EWS 0	1.00	0.97 – 1.02	0.80
Oxygen saturation EWS 1	0.99	0.97 – 1.00	0.15
Oxygen saturation EWS 2	0.92	0.85 – 0.98	0.03
Oxygen saturation EWS 3	0.94	0.80 – 1.03	0.29

**Due to limited variation in the HR data, the upper limit of the CI could not be calculated. CI: confidence interval.*

Supplementary figure 1. Example plot of TWA RR in the 4-hour period before clinical deterioration.



Example of time weighted average (TWA) for RR. The TWA combines the duration and severity, i.e. EWS score 0 – 3, divided by total measured monitoring time. First, the area under/above the threshold (AUT) is calculated for this 12 minute period.
*The AUT in the example above is: (EWS 0 x 4 min) + (EWS 1 x 2 min) + (EWS 2 x 3 min) + (EWS 3 x 4 min) = 20 EWS*min*
Then, the AUT is divided by the total measured monitoring time, which in this example was 12 minutes.
TWA = 20 ÷ 12 min = 1.67 EWS. This means that over this 12 minute period, the average EWS was 1.67.
In case of any missing vital sign values, the number of missing measurements were subtracted from the total number of measurements in that time period. Thus, for example, in case the patient was out of bed for 30 minutes over the 240 minute period of interest, the AUT was divided by 210 minutes (e.g. 240-30).



Chapter 5

High risk medication and postoperative hypoxemia in frail elderly cardiac surgery patients:

a prospective observational study.

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ABSTRACT

Introduction

Opioids and benzodiazepines are widely used to treat postoperative pain and anxiety. Older patients are more susceptible for the depressant effects of high risk medication (HRM) including hypoxemia. This study investigated the association between HRM and postoperative hypoxemia in frail older cardiac surgery patients.

Methods

A prospective, single center study in frail patients undergoing elective cardiac surgery. Postoperative oxygen saturation (SpO_2) was continuously monitored for 72 hours at the general ward. Administration times of HRM were recorded for all patients. Primary endpoint was hypoxemia, defined as SpO_2 <90% for ≥10 minutes. The association between HRM and hypoxemia was assessed with the marginal means/rates model during 3 hours after drug administration (period of maximum treatment effect), and adjusted for EuroSCORE II. The overall incidence and duration below SpO_2 <95%, 90% and <85% were explored as secondary endpoints.

Results

HRM were administered to 51/70 (73%) patients. Postoperative hypoxemia occurred in 56 (80%) patients. Overall, patients with HRM had more hypoxemic episodes (336 versus 126 for patients without HRM, P <0.001) and spent more time below abnormal SpO_2 thresholds (1233 vs. 438 minutes, P = 0.58). However, during the period of maximum treatment effect HRM was not associated with recurrent hypoxemia (aRR 1.21, 95% CI 0.74 – 2.01, P=0.47).

Conclusion

Postoperative hypoxemia and administration of HRM are common in frail elderly patients recovering from cardiac surgery. Although patients with HRM experience more hypoxemic episodes, HRM was not associated with an increased risk of recurrent hypoxemia during the period of maximum treatment effect.

INTRODUCTION

Although the number of elderly patients scheduled for cardiac surgery is increasing rapidly, a substantial proportion experiences a postoperative complication. International studies show that especially frail elderly cardiac surgery patients are at increased risk of adverse postoperative outcomes, including morbidity, mortality and readmissions.[1–3] Episodes of hypoxemia occur frequently in the postoperative period at the general ward and are a strong indicator of clinical deterioration, which often precedes postoperative complications.[4–7] Prior studies in non-cardiac surgery patients using continuously pulsoximetry monitoring showed that prolonged postoperative hypoxemia was common at the surgical ward, and that spot check measurements underestimated the incidence and duration of hypoxemia.[7,8]

Postoperative treatment of pain and anxiety with high risk medication (HRM), including opioids and benzodiazepines, is common during recovery from cardiac surgery at the general ward. A primary concern with HRM dosing regimens is the small therapeutic window.[9–12] Both hypoventilation secondary to pain and drug induced respiratory depression may induce hypoxemia.[4,6,13] Although scientific data are lacking, frail elderly are likely at increased risk of HRM side effects compared to non-frail patients. Furthermore, disease related changes in organ function, polypharmacy and drug interactions make it harder to predict treatment effects.[13] Currently, limited data exists on vital outcomes including hypoxemia in frail older patients who use HRM. Evidence on the association between HRM and postoperative hypoxemia is needed to improve drug safety and effectiveness in frail elderly patients.[11,12,14–16]

We hypothesized that frail elderly cardiac surgery patients are at increased risk for postoperative drug-induced hypoxemia at the general ward. Therefore, the aim of this study was to investigate the association between postoperative hypoxemia and administration of opioids and benzodiazepines in frail elderly patients.

METHODS

Study design and population

The Anaesthesia Geriatric Evaluation (AGE) AWARE study was a prospective single center observational cohort study analyzing postoperative vital signs using continuous monitoring in frail elderly cardiac surgery patients.[17] Inclusion took place from March 2020 until December 2021 at the St. Antonius hospital, Nieuwegein, The Netherlands. Inclusion criteria were patients aged ≥ 70 years with clinical frailty scale (CFS)[18] ≥ 4, undergoing elective open cardiac surgery (**Supplementary figure 1**). Details on the AGE AWARE study were previously reported.[17] In short, vital signs were continuously monitored for 72 postoperative hours in all patients after arrival at the general ward using remote monitoring by the EarlySense system (EarlySense Ltd, Ramat Gan 5252007, Israel). Ethical approval was provided by the local ethics committee on September 2019 for the research proposal: "Postoperative remote monitoring of vital signs in older cardiac surgery patients" (Medical Research Ethics Committees United, no. R19.018). The study was registered at clinicaltrials.gov (identifier: NCT03944967) and performed in accordance with the Declaration of Helsinki. All patients provided written informed consent. This manuscript adheres to the STROBE guidelines.[19]

High risk medication

As part of standard care all patients received oxycodone hydrochloride controlled-release (oxycontin) and oxycodone hydrochloride immediate-release (oxynorm) according to a standardized postoperative pain protocol. Pain was assessed by self-report with the Numeric Rating Scale (NRS) for pain (0 = no pain at all and 10 = worst imaginable pain).[20] If patients experienced pain (NRS ≥ 4), the standardized postoperative pain protocol was initiated. This included oxycontin 10 mg twice daily, oxynorm 5 mg as needed (maximum 6 times a day) during the first two days at the ward. On the third day opioids were reduced and only oxynorm 5 mg as needed was prescribed. If patients did not experience pain, oxycontin and oxynorm were not prescribed. Oxazepam and temazepam were administered at the discretion of the attending medical resident in cases of insomnia or anxiety. For this study, administration of oxycontin, oxynorm, oxazepam and temazepam were considered high risk medication (HRM), which we subsequently analyzed as binary variable.

The Tmax of a medication represents the moment at which the drug concentration peaks, presenting the highest potential for adverse effects, such as drug-induced hypoxemia. The Tmax for each HRM was retrieved from the summary of product characteristics: 50 minutes for temazepam, 1.5 hours for oxynorm, 2.5 hours for oxycontin and 2 to 3 hours for oxazepam. To ensure that we accounted for the

maximum treatment effect of HRM we choose a period of 3 hours as reference. We will use the term "period of maximum treatment effect" to denote the time frame from drug administration until 3 hours thereafter.

Continuous oxygen saturation monitoring

After arrival at the general ward, oxygen saturation (SpO_2) was continuously monitored for 72 hours or until hospital discharge, death or readmission to the intensive care unit (ICU). SpO_2 was measured with a pulsoximeter by the EarlySense system (EarlySense Ltd, Ramat Gan 5252007, Israel). SpO_2 was measured as long as the patient remained connected. Patients and healthcare professionals were blinded for continuous SpO_2 data. Artefacts of SpO_2 measurements were identified and labeled as missing, when values were outside physiological ranges (i.e. SpO_2 < 60% or > 100%). If patients had missing SpO_2 values for a time period < 5 minutes, the last measured value was carried forward. If a period of missing values lasted ≥ 5 and < 10 minutes, we calculated the average of the last measured values at the beginning and end of this period and altered the missing value into this average. If a period of missing values exceeded 10 minutes, all values were coded as missing.

Data collection

Data were collected from electronic health records, Epic (Epic Systems Corporation, Verona, WI, USA). This included demographics, medical history, health status, comorbidities, CFS[21], previous surgical procedures, laboratory tests and data of HRM administration for the duration of the study period. Frailty was categorized according to the CFS into very mild frailty (CFS = 4), mild frailty (CFS = 5) and moderate to severe frailty (CFS ≥ 6).[21] To assess the overall burden of comorbidities, the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) was calculated for each patient.[22] Registered data for continuous monitoring on SpO_2 was retrieved from the continuous monitoring system. All data was managed using the Research Electronic Data Capture (REDCap) system (Vanderbilt University, Nashville, TN, USA).[23]

Outcomes

The primary outcome was hypoxemia, defined as SpO_2 < 90% for ≥ 10 minutes. Secondary outcomes were incidences and duration of abnormal SpO_2 (i.e. <90%, <85% and <80%).

Sample size analysis

Based on prior literature reports on remote monitoring of postoperative vital signs in major non-cardiac surgery patients, hypoxemia (defined as a SpO_2 <90% for 1 hour) occurred in 37% of study patients.[7] It seems reasonable to assume that in our

cohort of older cardiac surgery patients the incidence of hypoxemia may be similar, or even worse. Our pilot study enrolled 70 patients, based on practical feasibility and in accordance with other pilot studies on remote monitoring of vital signs in postoperative patients.[24,25] With 70 patients and an expected incidence of hypoxemia of at least 37%, we were confident to be able to assess the shape and magnitude of the associations between medication risk factors and hypoxemia in order to test those hypotheses. This sample size deviates from the originally registered in the protocol at clinicaltrials.gov, as a result of prolonged slow patient enrollment due to a declining operating room program.

Statistical analysis

Differences between patients with and without HRM were tested using the independent T-test or Mann-Whitney U test for continuous variables or a chi-square test or Fisher's exact test for categorical variables. Patient differences are presented as frequencies and percentages (%) for dichotomous and categorical data and for continuous data as median with interquartile range (IQR). To evaluate overall SpO_2, the duration in mean minutes per hour spent below abnormal SpO_2 thresholds (i.e. <90%, <85% and <80%) was calculated and summarized in incidence curves. Subsequently, the duration in mean minutes per hour spent below each threshold was compared between patients with and without HRM. As SpO_2 measurements were missing for 52% of the time, we conducted a sensitivity analysis without missing data to avoid potential underestimation of hypoxemia.

To evaluate hypoxemia, the overall incidence and number of hypoxemic episodes over time, were calculated and summarized for patients with or without HRM. Within the 72-hour monitoring period, the primary outcome may occur multiple times per patient. The association between the period of maximum treatment effect of HRM and hypoxemia was assessed with a marginal means/rates model.[26] This model is a semiparametric extension of the Cox proportional hazard model and accounts for recurrent hypoxemic episodes that may have occurred within the same patient. It allowed us to estimate the mean number of hypoxemic episodes, while accounting for the repeated nature of the measurements within individuals over time. HRM was added as time-varying covariate to the model, extending from administration until the longest Tmax, as HRM could have been administered multiple times during the monitoring period. The association was adjusted for EuroSCORE II to take age, sex, comorbidities and weight of the procedure into account. This confounder was a priori selected based on clinical relevance, anticipating that patients in poorer health undergoing complex surgeries would likely require postoperative medication and could be at higher risk for hypoxemia. To estimate the effect of EuroSCORE II on the occurrence of hypoxemia

in patients with or without HRM, we introduced an interaction term denoted as 'HRM * EuroSCORE II' into the marginal means/rates model. This interaction allowed us to examine whether the impact of HRM on hypoxemia varied depending on different values of EuroSCORE II. Estimates for these associations are expressed as rate ratios (RRs) with corresponding 95% confidence intervals (CI). The analysis was conducted using R statistics version 4.1.0 running under R studio version 1.4.1717.

RESULTS

Patient population

This study included 70 patients (**Supplementary figure 1**). Median age was 75 years (IQR 74 – 77). Fifty-six percent of patients (39/70) had very mild frailty (CFS = 4), 37% of patients (26/70) mild frailty (CFS = 5) and 7% of patients (5/70) had moderate to severe frailty (CFS ≥ 6). Baseline characteristics for patients with and without HRM are presented in **Table 1**. Median monitoring time of SpO_2 was 72 hours (IQR 52 – 72 hours). During monitoring, all patients received supplemental oxygen therapy at some point, with a median amount of 2L/h (IQR 1 – 3 L/h). SpO_2 measurements were missing 52% of the time. During daytime (6 AM until 10 PM), there were slightly more missing data compared to nighttime (53% vs. 47%). The main reason for missing data during the day was improved mobility and during the night it was disconnection from the pulsoximeter.

Table 1. Baseline characteristics

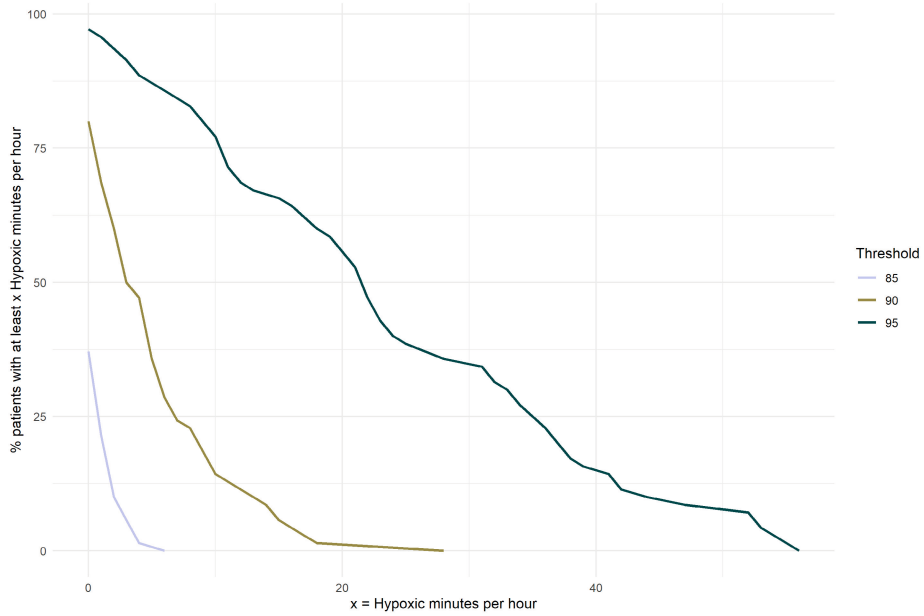
Patient characteristics	HRM (n = 51)	No HRM (n=19)	P-value
Sex, male/female sex	14/37 (28%/72%)	7/12 (37%/63%)	0.64
Age, yrs	75 (73.5 – 77.0)	76 (74.5 – 79.0)	0.18
EuroSCORE II	1.65 (1.33 – 2.77)	2.01 (1.83 – 3.95)	0.04
Clinical Frailty Scale			0.63
4	30 (60%)	9 (47%)	
5	18 (35%)	8 (42%)	
6 or more	3 (6%)	2 (11%)	
Type of surgery			
Single CABG	21 (41%)	5 (26%)	0.39
Single valve	19 (37%)	2 (11%)	0.06
Aortic surgery	2 (4%)	1 (5%)	1.00
Combined surgery	9 (18%)	11 (58%)	0.003
Duration of surgery, min	184 (157 – 215)	205 (174 – 256)	0.16
Length of stay ICU, days	1 (1 – 1)	1 (1 – 3)	0.01
Readmission ICU	4 (8%)	1 (5%)	1.00
Length of hospital stay, days	7 (6 – 9)	9 (7 – 11)	0.02

Continuous variables reported as median (IQR), categorical variables as frequency (%).
n/no.: number; yrs: years; CABG: coronary artery bypass grafting; ICU: intensive care unit.
HRM: high risk medication (i.e., oxycontin, oxynorm, oxazepam, temazepam).

Hypoxemia

Fifty-six (80%) patients experienced one or more episodes of hypoxemia. The median number of hypoxemic episodes was 7 (IQR 4 – 11). Hypoxemia occurred more frequently during the day (6 AM until 10 PM) compared to nighttime (58% vs. 42% respectively, P<0.001). The incidence of hypoxemia decreased over time, with 39% occurring during the first 24 hours after arrival upon the general ward and decreasing to 21% during the last 24 hours. Prolonged hypoxemic episodes were common, 40% of patients (28/70) had at least 1 episode lasting one hour or more, while 16% of patients (11/70) experienced episodes lasting 2 hours or more. **Figure 1** illustrates the incidence of patients with abnormal SpO_2 levels (respectively SpO_2 <95%, <90% and <85%). Twenty-five patients (35%) spent an average of 30 minutes per hour or more with SpO_2 levels <95%. Thirteen patients (19%) spent an average of at least 10 minutes per hour with SpO_2 levels <90%. **Supplementary figure 2** demonstrates the incidence curves without missing data.

Figure 1. Incidence curves of duration in mean minutes per hour spent with abnormal SpO_2 levels.



Incidence of patients with an average number of minutes per hour with abnormal SpO_2 levels during monitoring (SpO_2 *<95%,* SpO_2 *<90% and* SpO_2 *<85%). HRM: high risk medication.*

High risk medication and hypoxemia

Fifty-one patients (73%) received HRM and 26% of patients received both opioids and benzodiazepines during hospital stay. **Table 2** summarizes information on medication administration per HRM type. Half of all HRM was administered during the first 24

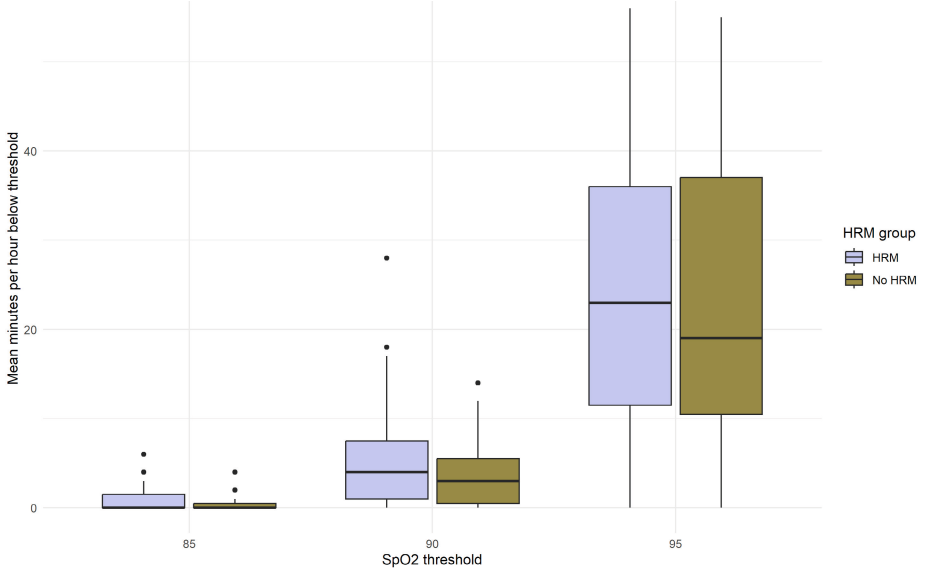
hours after admission at the general ward. During the period of maximum treatment effect, HRM was not associated with an increased risk of recurrent hypoxemia (adjusted RR 1.21, 95% CI 0.74 – 2.01, P=0.47). However, patients with HRM had more hypoxemic episodes (336 versus 126 episodes for patients without HRM, P < 0.001) and spent more time with abnormal SpO_2 levels **(Figure 2)**.

Table 2. High risk medication

High risk medication type	Total no. of patients	Total no. of gifts	Median no. of gifts per patient	Median dose per gift (mg)	Individual total amount per admission (mg)
Oxycontin	43 (61%)	127 (39%)	3 (2 – 4)	5 (5 – 10)	15 (10 – 30)
Oxynorm	45 (64%)	157 (48%)	3 (2 – 5)	5 (5 – 5)	15 (10 – 25)
Oxazepam	13 (19%)	27 (8%)	2 (1 – 3)	10 (10 – 10)	20 (10 – 30)
Temazepam	8 (11%)	15 (5%)	2 (1 – 2)	10 (10 – 10)	15 (10 – 23)

Continuous variables reported as median (IQR), categorical variables as frequency (%).
no.: number; mg: milligram.

Figure 2. Duration in mean minutes per hour spent with abnormal SpO_2 levels for patients with or without HRM.



Duration in mean minutes per hour spent with abnormal SpO_2 levels during monitoring for patients with and without HRM (SpO_2 *<95%,* SpO_2 *<90% and* SpO_2 *<85%). HRM: high risk medication.*

DISCUSSION

This study on postoperative hypoxemia and administration of HRM demonstrates several new findings. First, 80% of frail elderly patients experience hypoxemia after ICU discharge following cardiac surgery despite oxygen suppletion. Second, 73% of patients received HRM during postoperative recovery, and 26% used a combination of opioids and benzodiazepines. Third, despite more hypoxemic events, HRM was not associated with increased risks of recurrent hypoxemia in frail patients during the three-hour period of maximum treatment effect.

Previous studies have demonstrated a high incidence of hypoxemic events in the postoperative period.[4-7] However, SpO_2 levels measured with spot check monitoring by nurses seriously underestimate the incidence and severity of hypoxemia.[7,27] As hypoxemia is potentially associated with increased risks of adverse postoperative outcomes, such as myocardial ischemia and respiratory failure, suboptimal monitoring may increase failure to rescue.[4] On a general ward, spot check measurements are performed once every eight hours to evaluate a patients' medical condition. Nonetheless, patients are most of the time unmonitored and spot checks by nurses usually induce arousal, thereby potentially (partly) restoring SpO_2 levels in patients with hypoxemia.[28,29] Henceforth, we chose to continuously monitor SpO_2 levels in the frail elderly population following cardiac surgery after arrival at the general ward. Previous studies in postsurgical populations using continuous monitoring reported incidences of hypoxemia varying from 12% to 56%.[28,30,31] While some of these studies focused on high-risk populations, such as cardiothoracic surgery patients or patients receiving postoperative opioids, the incidence of hypoxemia in our study is significantly higher. Yet, our study specifically targeted frail elderly following cardiac surgery. Frail elderly often have multiple underlying comorbidities and use a significant amount of medication, which, in general, increases the risk of postoperative complications such as pain, pneumonia and delirium, all of which can, in turn, lead to hypoxemia. Additionally, continuous SpO_2 data was blinded for patients and health care professionals in our study, meaning that desaturation could not trigger interventions. Therefore, the reported hypoxemia may better reflects the true extent of hypoxemic exposure in this high risk population.

The Anesthesia Patient Safety Foundation has recommended that "Intermittent 'spot checks' of oxygenation (pulsoximetry) and ventilation (nursing assessment) are not adequate for reliably recognizing clinically significant evolving drug-induced respiratory depression in the postoperative period", and that "Continuous electronic monitoring of oxygenation and ventilation would reduce the likelihood of unrecognized

clinically significant opioid-induced depression of ventilation in the postoperative period".[27] Respiratory depression due to overdosing is thought to be the most important adverse effect of high risk medication such as opioids and benzodiazepines during postoperative recovery.[14,16,28,32,33] Different criteria have been used to define respiratory depression including ventilator frequency, percutaneous oxygen saturation, arterial blood gas analysis, and the need to administer oxygen stimulants.[34] In a postsurgical population of patients receiving patient-controlled analgesia (PCA), 12% of patients had episodes of respiratory depression (SpO_2 values < 90%; i.e. hypoxemia) lasting 3 minutes or more, while receiving supplemental oxygen.[31] In a different study to nocturnal oxygenation during PCA, 56% of patients breathing room air experienced hypoxemia and 13% of patients with oxygen supplementation experienced hypoxemia.[30] As far as we know, there are no studies on the association between oral administration of HRM (i.e. opioids and benzodiazepines) and postoperative hypoxemia. In our study, we did not found an increased risk of recurrent hypoxemia within the maximum treatment effect period of oral HRM. A possible explanation might be that it was unclear whether oxygen suppletion therapy was increased after administration of HRM in our study. Although different studies have repeatedly shown that oxygen therapy decreases postoperative hypoxemia in patients receiving narcotics, patients receiving oxygen suppletion in our study and in the previous studies on patients receiving PCA, still experienced hypoxemic episodes.[30] Therefore, an alternative explanation could be that patients receiving HRM may be in poorer health. To account for the potential differences in patient health, we corrected for EuroSCORE II. Nevertheless, we are unable to draw clear conclusions that the period of maximum treatment effect of HRM has no impact on the risk of hypoxemia. However, it is worth noting that patient receiving HRM showed a higher occurrence and longer duration of hypoxemia than patients without HRM. These results demonstrate the associated risk of receiving HRM.

Various studies have demonstrated the challenges of dosing HRM, particularly in elderly patients, where rational prescribing is complex due to heterogeneity in drug disposition, comorbid medical conditions, polypharmacy, or changes in body composition and analgesic response.[13] The individual total amount per admission per patient in our study population was low (i.e., 15 mg for oxycontin and oxynorm, 20 mg for oxazepam and 15 mg for temazepam). Nonetheless, a higher incidence and longer duration of hypoxemic episodes occurred within patients receiving HRM. In general, it is recommended to 'start low and go slow' in the geriatric population with HRM to prevent adverse drug effects, due to the small therapeutic range which carries a greater risk of over- or underdosing.[13] However, clearly effects of age and frailty on the therapeutic window remains unclear. There is still too little evidence that can fully explain the observation that older people are more sensitive to the therapeutic and

adverse effects of HRM and dose adjustments. Therefore, careful monitoring is an essential requirement when using HRM for pain and anxiety.

There are some limitations to address. Due to the nature of the monitoring system, SpO_2 levels were only measured when the pulsoximeter was attached to the patients' finger, leading to a substantial amount of missing data in our study. Additionally, patients who recovered well discontinued continuous monitoring, which might have led to attrition bias. In light of these considerations, and given our analysis of a high risk population, the reported incidence of hypoxemia may potentially result in an overestimation of hypoxemia exposure within the frail postoperative population.

Conclusions

In summary, hypoxemia is common in frail elderly patients recovering from cardiac surgery. While patients receiving HRM have more hypoxemic episodes, there is no association between HRM and hypoxemia during the period of maximum treatment effect.

ACKNOWLEDGEMENTS

None

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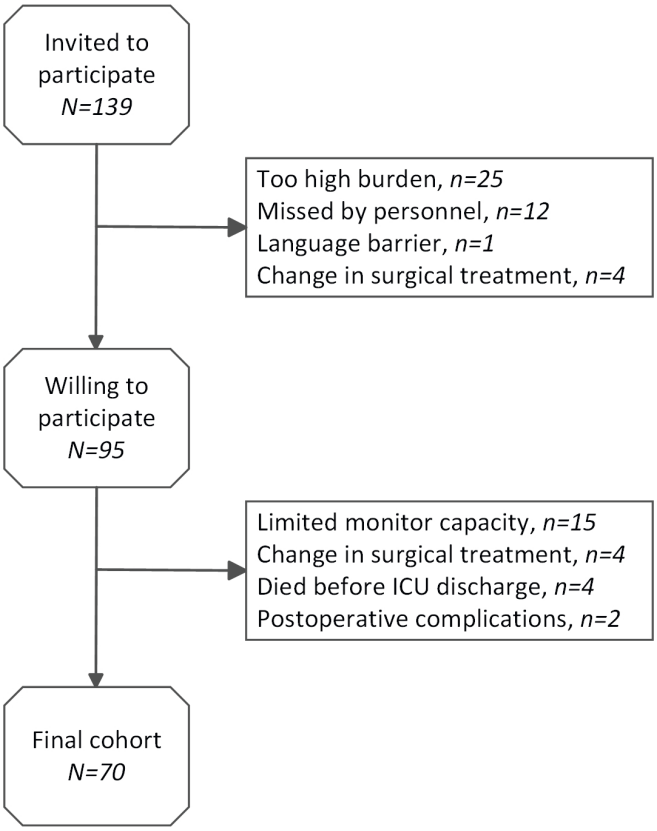
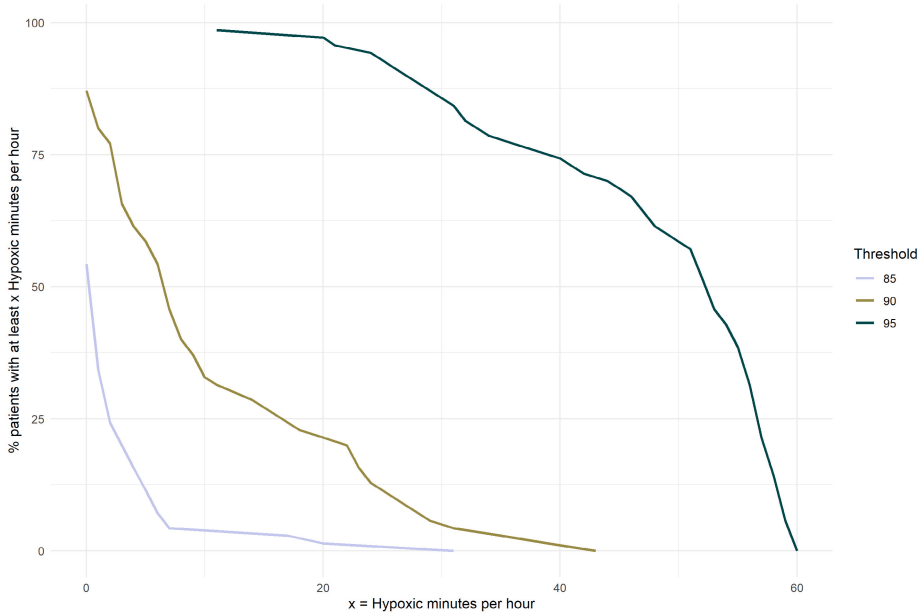
SUPPLEMENTARY MATERIAL

Supplementary figure 1. Schematic flowchart AGE AWARE study.



Supplementary figure 2. Incidence curves of duration in mean minutes per hour spent with abnormal SpO_2 levels, without missing data.



Incidence of patients with an average number of minutes per hour with abnormal SpO_2 levels during monitoring (SpO_2 <95%, SpO_2 <90% and SpO_2 <85%) without missing data. HRM: high risk medication.

Chapter 6

Pharmacokinetics and analgesic response of morphine and morphine-3-glucuronide in frail older patients undergoing cardiac surgery.

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ABSTRACT

Introduction

Acute postoperative pain management is challenging in frail older patients due to their susceptibility to adverse effects of opioids. This study compared the pharmacokinetics (PK) of morphine and morphine-3-glucuronide (M3G) in frail elderly cardiac surgery patients with a general intensive care unit (ICU) population consisting of postcardiac surgery and critically ill patients. Secondly, we studied the analgesic response to a standardized postoperative morphine treatment protocol in the ICU.

Methods

Using a previously published population model, external validation and simulations were performed to explore differences in PK in frail elderly patients (i.e., ≥ 70 years with Clinical Frailty Scale ≥ 4) versus general ICU patients. For the analgesic response to standardized morphine treatment (2 mg/h), clinically driven dose adjustments were analysed in conjunction with corresponding individual morphine and M3G concentrations, postoperative severe pain (i.e. Numeric Rating Scale (NRS) ≥ 4) and oversedation.

Results

In total, 237 morphine and M3G concentrations were analysed from 22 frail elderly patients after cardiac surgery. In frail elderly, morphine glucuronidation remained unchanged, morphine clearance through other routes showed a 39% decrease and M3G elimination showed a 43% increase, compared to general ICU patients. These differences result in an increased morphine exposure of approximately 20%. In 4 patients (18%), analgesic response was satisfactory, without requiring dose adjustment due to oversedation or severe pain. 18 patients (82%) experienced oversedation and 11 patients (50%) experienced severe pain at least once. The correlations between morphine concentration or M3G concentration and NRS scores were weak ($r = -0.25$, $p=0.06$ for morphine and $r = -0.07$, $p=0.6$ for M3G).

Conclusion

In frail older cardiac surgery patients, morphine glucuronidation was similar to general ICU patients, but morphine clearance through other routes was decreased and M3G elimination increased. Analgesic response to standardized morphine treatment varied substantially and was only satisfactory in a minority of patients.

INTRODUCTION

Moderate or severe postoperative pain after cardiac surgery is associated with complications and risk of chronic pain. Up to one third of older patients experience postoperative pain, especially when frailty is present.[1–4] Optimal dosing of morphine in older surgical patients is difficult due to physiological changes associated with aging and frailty.[2,4–7] These changes may cause altered pharmacokinetics (PK) and pharmacodynamics (PD), leading to poor pain management and side effects, including oversedation or apnoea.[8–13]

Although the PK of morphine and its metabolites are widely studied in the general population, evidence is limited on the PK-PD relationship of morphine in frail elderly following cardiac surgery. Previously, a PK model for morphine and morphine-3-glucuronide (M3G) was developed in a general Intensive Care Unit (ICU) population consisting of cardiac surgery and critically ill patients.[14] For ICU patients with normal creatinine concentrations, a decrease of 76% was estimated in M3G elimination clearance compared to healthy subjects, which results in substantial accumulation of M3G over time.[14]

This study compares the PK of morphine and M3G in frail elderly patients after cardiac surgery to a general ICU population.[14] Additionally, we studied the analgesic response to a standardized morphine treatment using clinically driven dose adjustments in conjunction with morphine and M3G concentrations.

METHODS

Study design and population

The Anaesthesia Geriatric Evaluation (AGE) AWARE II study was a single centre, prospective, cohort study in the Netherlands (St. Antonius Hospital, Nieuwegein). Inclusion took place from October 2020 until November 2021. Patients aged ≥ 70 years with a Clinical Frailty Scale ≥ 4[15] undergoing elective open cardiac surgery were eligible to participate. Patients with a contraindication for morphine were excluded. Ethical approval was provided by the local ethics committee before patient recruitment (Medical Ethics Research Committees United (www.mec-u.nl), number R20.015). The study was registered at ClinicalTrials.gov (NCT04696445) and performed in accordance with the Declaration of Helsinki. All participants provided written informed consent. This manuscript adheres to the STROBE guidelines.[16]

Anesthesia and standardized postoperative pain management with morphine

Perioperative care was routinely performed according to local standardized procedures. For intraoperative analgesia, a continuous infusion of remifentanil was initiated after induction of anesthesia and intermittent fentanyl doses were used at predetermined times (i.e., prior to incision of the skin, sternotomy, aorta cannulation, and opening of the pericardium). Doses were determined at the discretion of the attending anesthesiologist, depending on patient characteristics and intraoperative vital parameters. All patients received a loading dose of 10 mg intravenous morphine 30 minutes before the anticipated end of surgery. Postoperatively, all patients stayed in the ICU for one night before being transferred to the general ward for further recovery. On admission to the ICU, a continuous morphine infusion of 2 mg/h was started. Pain was assessed by self-reported Numeric Rating Scale (NRS) for pain (ranging from 0 = no pain at all to 10 = worst imaginable pain).[17] The NRS was scored at least once every 4 hours, except when patients were asleep without evidence of pain. If patients had severe pain (NRS score ≥ 4), additional intravenous bolus doses (2.5 to 7.5 mg) of morphine were administered and/or maintenance doses were increased, based on the discretion of treating physicians. Similarly, in case of anticipated delayed arousal or oversedation, the morphine infusion rate could be reduced or stopped.

Data collection

Demographics were derived from the electronic health record (EHR), Epic (Epic Systems Corporation, Verona, WI, USA). This included health status, comorbidities, medication history, clinical frailty scale (CFS), previous surgical procedures, laboratory tests. Frailty was categorized according to the CFS into very mild frailty (CFS 4),

mild frailty (CFS 5) and moderate to severe frailty (CFS ≥ 6).[15] To assess the overall burden of comorbidities, the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) was calculated.[18] Data on opioid consumption and analgesic response, including use of naloxone, and NRS scores were extracted from the EHR. All data was gathered and managed using the Research Electronic Data Capture (REDCap) system (Vanderbilt University, Nashville, TN, USA).[19]

Blood sample collection and analysis for pharmacokinetic modelling

In all patients, 2 mL arterial blood samples were drawn at t = 20 – 60, 120, 180, 240, 420, and/or 480 minutes after the first dose of intravenous morphine administered at the end of surgery. In addition, blood samples were collected in case of deviations from the standardized treatment with morphine (i.e. when morphine was decreased or stopped due to oversedation, or increased due to severe pain). The exact timing of each blood sampling was documented. The blood samples were placed in EDTA tubes until separated by centrifugation (4000 rpm for ten minutes) and stored at – 80 °C until analysis. All samples were analysed for serum concentrations of morphine and M3G using high-performance liquid chromatography tandem mass spectrometry.[20] The lower limit of quantification (LLOQ) was 2 µg/L for both morphine and M3G. In total, 11% (14 of 126) of the morphine concentrations and 0.8% (1 of 126) of the M3G concentrations were below the LLOQ; these concentrations were omitted from the PK analysis. The M3G concentrations were expressed as micrograms of morphine base units per L, logarithmically transformed and fitted simultaneously with logarithmically transformed morphine concentrations.

Sample size

To calculate the sample size of this study, we used the M3G elimination clearance for which a significant difference was seen between the ICU population compared to healthy volunteers as reported in the previously published model.[14] The average M3G elimination clearance and standard deviation was 0.573 (0.313) L/min. The M3G clearance in ICU patients with normal renal function was 76% decreased compared to healthy volunteers. Assuming that these data are normally distributed, the sample size was calculated with a Student's t-test. Using a level of significance of 0.05 and a power of 0.8, 20 subjects were included to be able to detect a 35% difference in M3G clearance between frail elderly and a general ICU population.

Pharmacokinetic analysis

Population model validation was performed using nonlinear mixed effects modelling software (NONMEM), version 7.4.3 (Icon Development Solutions, Hanover, MD, USA) running under Pirana version 3.0.0 (University of Uppsala, Sweden). The NONMEM

output was analysed using R version 4.1.0 running under Rstudio version 1.4.1717 (R foundation for Statistical Computing, Vienna, Austria).

The previously published population pharmacokinetic model that was used, was developed using 3012 morphine and M3G concentrations from 117 cardiac surgery patients and 18 critically ill patients from the ICU (hereafter referred to as the general ICU population), and 20 healthy volunteers.[14] In this model, a 3-compartment model was used to describe the disposition of morphine and a 1-compartment model for M3G. The schematic representation of the structural model is shown in **Supplementary figure 1**. Morphine clearance was quantified through the formation of the M3G metabolite ($CL_{m,M3G}$) as well as through other routes ($CL_{non\text{-}M3G}$), which includes amongst other unchanged renal elimination and formation of morphine-6-glucuronide. For M3G, a single elimination clearance was quantified ($CL_{e,M3G}$). Log-normally distributed inter-individual variability was quantified for all three clearance parameters as well as for the distribution volume of M3G.

In the current analysis, the previously published model[14] was externally validated in frail elderly undergoing cardiac surgery to assess whether the PK of morphine and M3G was similar to general ICU patients. This external validation was based on the obtained PK parameter values for general ICU patients. Since, contrary to the general ICU patients, our frail elderly patients did not have renal failure, the covariate relationship between serum creatinine concentrations and the M3G elimination clearance was not taken into consideration by fixing all values for creatinine concentration in the elderly at 80 μmol/L. **Supplementary table 1** lists all parameter estimates of the original model of Ahlers et al.[14] Individual post hoc parameter values and predicted morphine and M3G concentrations were then obtained using a Bayesian estimation (i.e., MAXEVAL=0). The obtained output was visually assessed in goodness-of-fit plots for morphine and M3G (observed *versus* population-predicted concentrations and conditional weighted residuals (CWRES) *versus* time and *versus* population predictions). Individual deviations from typical parameter values (i.e., eta-values) were plotted independently versus covariate values, to visualize potential correlations. Then, using a combined dataset of general ICU patients[14] and frail elderly from the current study, deviating values were estimated for frail elderly for each model parameter while keeping the other parameters fixed to the values for general ICU patients, to assess potential differences between frail elderly and the general ICU population. Discrimination between the different models was made by comparison of the objective function value (OFV, i.e., -2 log likelihood). A decrease of 3.84 points in the OFV for one degree of freedom was considered statistically significant, representing a p-value < 0.05. Moreover, the optimized model was assessed by inspection of the aforementioned

goodness-of-fit plots and relative standard errors of the parameters estimates being <50%. Finally, the proportional deviation between the newly estimated parameter values in the optimized model and the original parameter estimates was calculated. To assess the predictive properties of the optimized model in frail elderly, a normalized prediction distribution error (NDPE) analysis was performed using the NDPE package in R. Each observed concentration was visually and numerically compared to 1,000 simulated values.

Model-based simulations

Simulations using the optimized final model were conducted to illustrate the difference in concentration-time profiles of morphine and M3G upon the applied morphine treatment in frail elderly patients compared to the general ICU population. Using this model, simulations were performed in a typical individual from the general ICU population and a typical frail elderly patient with creatinine levels of 80 μmol/L. Two scenarios were simulated for each typical patient, 1) a 10 mg intravenous bolus dose of morphine, and 2) a continuous 2 mg/h morphine infusion over 72 hours.

Analgesic response to standardized morphine treatment

To evaluated whether patients received satisfactory morphine treatment, we evaluated the analgesic response at the ICU over time. Analgesic response was considered satisfactory if the morphine infusion rate maintained at 2 mg/h throughout the ICU stay, or was gradually decreased in case of low pain scores. Analgesic response was considered inadequate if; a) the infusion rate was reduced or stopped, due to delayed arousal or when treatment with naloxone was given (i.e. oversedation); or b) the infusion rate was increased, due to severe pain. To assess whether inadequate analgesic response corresponded with the concentrations of morphine and/or M3G in frail elderly patients, the observed concentrations of morphine and M3G were plotted against NRS pain scores. Only NRS pain scores and blood sample collections taken within 90 minutes of each other were included for analysis. The correlation between observed concentrations and NRS was evaluated using the Spearman rank-order correlation coefficient. The Spearman's correlation coefficient was considered weak (0 – 0.3), moderate (0.4 – 0.6) or strong (0.7 – 1). Descriptive statistics of patients characteristics were reported as means with standard deviations (SDs), median with interquartile range (IQR), and proportions. A p-value < 0.05 was considered statistically significant.

RESULTS

Population

This study included 22 frail older cardiac surgery patients. Median age was 75 years (IQR 74 – 77). Half of all patients were very mildly frail (CFS 4) and two (9%) patients had moderate to severe frailty (CFS ≥6). Coronary artery bypass surgery and single valve surgery were the most commonly performed procedures (**Table 1**). The median observation period was 22 hours (IQR 18 – 28 hours, range 2 - 74 hours), with a median number of 6 samples per patient. The median length of hospital stay was 7 days (IQR 7 – 10).

Table 1. Patient characteristics and data (n = 22 patients)

Patient characteristics and data (n = 22 patients)	
Sex, male/female sex	18/4 (82%/18%)
Age, yrs	75 (74 – 77)
Weight, kg	90 (85 – 107)
BMI (kg/m^2)	30 (28 – 34)
EuroSCORE II	1.6 (1.3 – 3.3)
Clinical frailty scale	
4	11 (50%)
5	9 (41%)
6 or more	2 (9%)
Preoperative creatinine concentration (µmol·L)	97 (82 – 109)
Type of surgery	
Single CABG	11 (50%)
Single valve	5 (23%)
Aortic surgery	1 (5%)
Combined surgery	5 (23%)
Duration of cardiopulmonary bypass, min	91 (76 – 99)
Cumulative intraoperative fentanyl, µg	1500 (1500 – 2000)
Cumulative intraoperative remifentanyl, µg	1850 (1450 – 2100)
Cumulative morphine administration, mg	31 (22 – 37)
Of which administered as bolus, mg	10 (5 – 10)
Morphine sampling period, hours	22 (18 – 28)
Number of samples (morphine, M3G)	
Total	252
Per patient	6 (5 – 7)

Continuous variables reported as median (IQR), categorical variables as frequency (%).
BMI: body mass index; CABG: coronary artery bypass grafting; NRS: numeric rating scale

Morphine pharmacokinetics

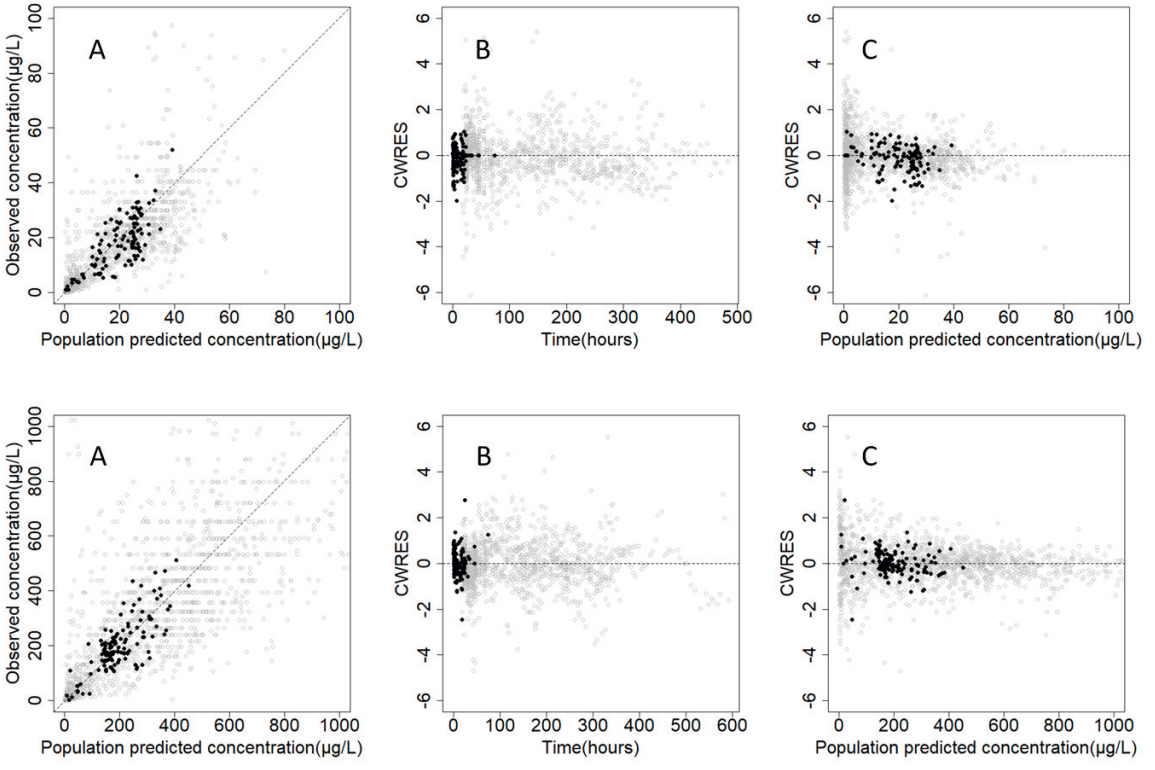
The analysis was based on 237 morphine and M3G perioperative serum concentrations. Standard goodness of fit plots obtained after fixing all parameters to values of the original model by Ahlers et al[14] showed reasonable accuracy (**Supplementary Figure 2)**. This figure shows that observed morphine and M3G concentrations of the frail elderly fell within the variability observed in the general ICU population, even though some biases could be observed. For the distribution of individual parameters from the typical parameter values (i.e., eta-values), clearance of morphine through other routes ($CL_{non\text{-}M3G}$) and M3G elimination clearance ($CL_{e,M3G}$) showed trends towards decreased and increased values compared to general ICU patients, respectively (**Supplementary Figure 3**).

When comparing parameter values for frail elderly patients with the general ICU population, morphine glucuronidation clearance was found to not be statistically significantly different, whereas clearance of morphine through other routes and M3G elimination clearance were different ($p<0.01$). All parameter values are summarized in **Supplementary table 1.** The estimated value for clearance of morphine through other routes and M3G elimination clearance in the optimized model were 0.33 (RSE 13.6%) and 0.0605 (RSE 6.4%), respectively, implying a 39% decrease in clearance of morphine through other routes in frail elderly cardiac patients and a 43% increase for M3G elimination clearance compared to the general ICU population. No statistically significant differences for frail elderly in comparison with general ICU population in any of the other parameters were found.

The optimized model that included adjusted parameter values for morphine through other routes and M3G elimination clearance was found to describe the data of the frail elderly accurately, as confirmed by the goodness-of-fit plots (**Figure 1**). The NPDE analysis confirmed that the optimized model could also accurately predict the typical trend of the concentration profiles in frail elderly patients. However, there was a slight overprediction of the variability of high concentrations for morphine and low concentrations for M3G (**Supplementary figure 4**).

Figure 2 illustrates the impact of the differences between a typical frail elderly and a typical general ICU patient on the exposure of morphine and M3G based on two treatment scenarios, using the optimized model. The reduced clearance of morphine through other routes in frail elderly increased morphine exposure, which results in an increased steady state concentration with approximately 20% in frail elderly, compared to general ICU patients. The increased morphine exposure also resulted in a higher fraction being metabolized to M3G. This effect is counterbalanced by the increased M3G elimination clearance observed in frail elderly, but does tend to result in decreased M3G exposure upon prolonged treatment.

Figure 1. Goodness-of-fit plots for the optimized model consisting of adjusted parameter values for morphine clearance through other routes ($CL_{non\text{-}M3G}$) and M3G elimination clearance ($CL_{e,M3G}$)



(A) Observed concentrations versus population predicted concentrations. The dotted line indicates the line of unity. (B) Conditional weighted residuals (CWRES) versus time. (C) CWRES versus population predicted concentrations. Top row represents morphine concentrations, bottom row morphine-3-glucuronide concentrations. The black dots represent the frail elderly patients, the grey dots represents the general ICU population (i.e., post cardiac surgery and critically ill patients).

Analgesic response

In 4 patients (18%) analgesic response was satisfactory throughout the follow-up period. In 11 patients (50%) morphine infusion was increased at least once due to severe pain and in 18 patients (82%) morphine infusion was reduced or stopped at least once due to oversedation. Two of these patients (9%) were treated with naloxone. In total 11 patients (50%) experiences both episodes of severe pain and oversedation. **Figure 3** illustrates the observed morphine and M3G concentrations in relation to NRS. The analgesic response to standardized morphine treatment was highly heterogeneous among frail elderly. In addition, the correlations between morphine or M3G concentrations and NRS scores were weak (r = – 0.25, p=0.06 for morphine and r = – 0.07, p=0.6 for M3G).

Figure 2. Morphine (left panels) and M3G (right panels) concentrations over time in a typical individual from the general ICU population (purple) and a typical frail elderly patient (green), both with normal creatinin (i.e. 80 µmol/L), after a 10 mg intravenous bolus dose of morphine (top panels) and a 2 mg/h continuous infusion of morphine for 72 hours (bottom panels).

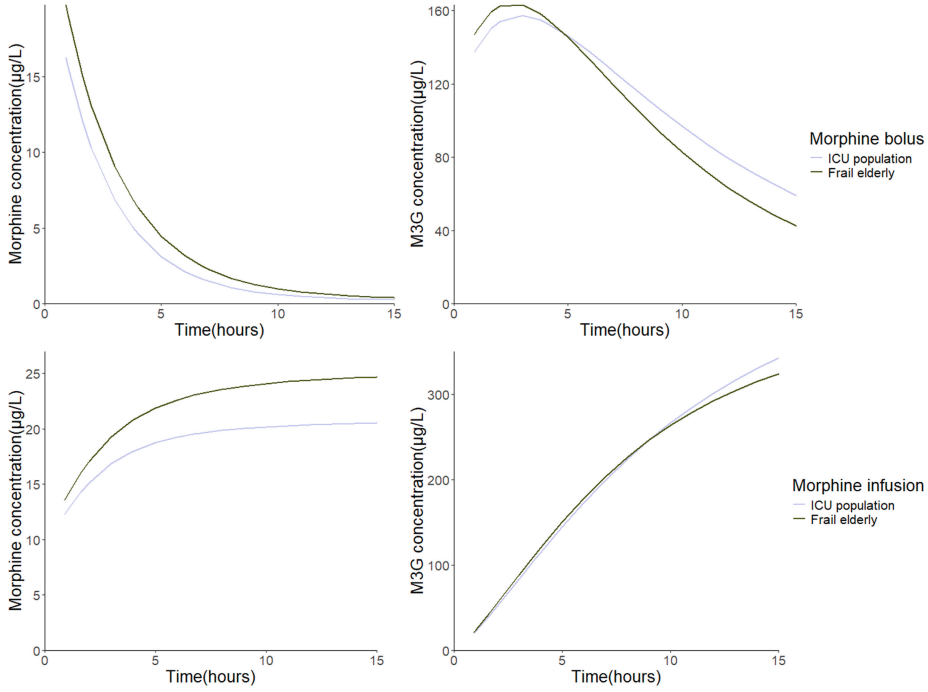
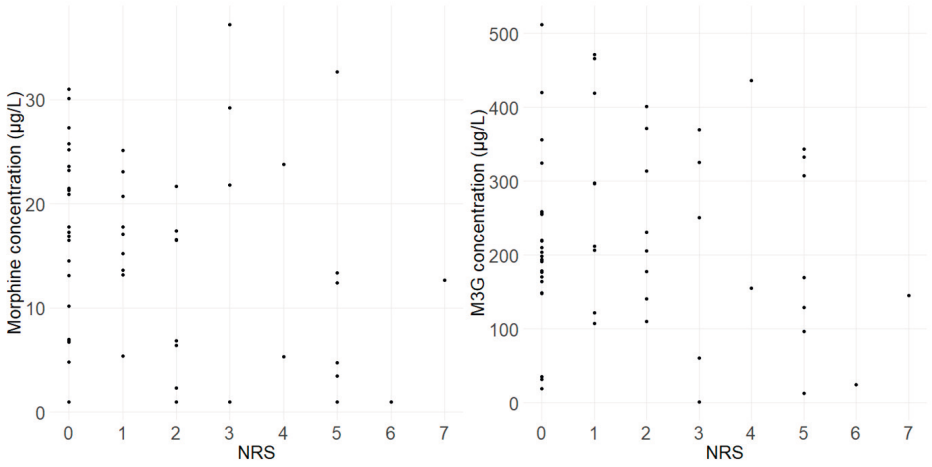


Figure 3. Morphine (left) and M3G (right) concentrations with corresponding NRS scores in frail elderly patients.



DISCUSSION

This study demonstrates that morphine glucuronidation after cardiac surgery in frail elderly is similar to general ICU patients, while elimination of morphine through other routes is decreased and M3G elimination is increased. As a result of these changes, a 20% increased steady state concentration of morphine can be expected. A satisfactory analgesic response was observed in merely one out of five patients, while the vast majority was oversedated. No correlation was found between observed morphine or M3G concentrations and NRS.

A few studies investigated the PK of morphine in non-surgical elderly volunteers (>60 years) and found reduced clearance of morphine and reduced distribution volumes compared to healthy young volunteers, resulting in higher peak plasma concentrations.[21–23] The results of our study showed that glucuronidation clearance was unaffected, elimination clearance of morphine through other pathways was reduced, and M3G elimination clearance was increased. As a result, a standard dosing regimen of 2 mg/h will give about 20% higher concentrations of morphine in frail elderly post-cardiac surgery compared to the general ICU population. In addition, the previous studies concluded that the increased sensitivity of elderly to the analgesic effects of morphine were at least partly due to an altered disposition and that these patients were at increased risk of adverse effects.[21–23] Our study found similar results, as the increased steady state concentration of morphine appeared clinically relevant in our population, because 82% of the patients experienced oversedation. Consequently, one could argue for lowering the infusion rate. However, healthcare personnel should be aware of an increased risk of postoperative pain when applying a lower dose. In our study, standardized pain management with morphine resulted in 50% of patients having severe postoperative pain for which doses of morphine were increased. Elderly patients who suffer from acute postoperative pain are at increased risk to develop chronic postoperative pain, and worse quality of life.[1,10] Given the substantial variation found in analgesic response within frail elderly in this study, it is essential to identify patient variables that are predictive of pain.

The weak correlation between pain scores and morphine concentrations in our study challenges current understandings in postoperative pain management. A previous study in 3.045 patients after various types of surgery (i.e. orthopaedic, urologic, abdominal, gynaecologic, vascular, thoracic, and cervicomaxillofacial), which evaluated the relationship between measurements of pain and morphine requirements during postoperative intravenous morphine titration, demonstrated that a visual analogue scale (VAS) score ≥ 70 predicted the need for a high dose of morphine (>0.15 mg/kg),

with an average dose of 12 ± 7 mg required for pain relief.[24] These results might give an indication of the amount of morphine needed to alleviate pain. In our study, however, the mean cumulative morphine per patient was 31 mg, while still 50% of patients experienced severe pain at some time point during the follow-up period. It should be noted that our population consisted of frail elderly following cardiac surgery, which is a painful procedure. Factors affecting pain relief and possible side effects experienced by the frail elderly patient are multitudinous. They include the pharmacokinetic variation among individuals, the possible effects of active metabolites, development of tolerance, differences in pain physiology and pharmacogenetics, dynamics of pain intensity, as well as psychological and social components.[25] Also, elderly patients may not adequately report pain scores, potentially leading to inadequate pain management. One of the major challenges is to gather quantitative information on all these variables for the development of larger pharmacokinetic models in which various drug and patient properties can be integrated. With such models, the PKPD and ultimately drug dosing of morphine can be predicted for individual frail elderly patients. Therefore, future research should focus on filling in these knowledge gaps to aid in the development of pharmacological models that can ultimately lead to personalized pain management.

This study has some limitations. The study included frail elderly patients with a short duration of morphine administration compared to the reference general ICU population that also evaluated patients with longer ICU stays. This may have restricted the scope of comparison, potentially affecting the generalizability of our findings, although the low values of the relative standard errors of the obtained parameter estimates doe suggest the findings to be adequately supported by the data. Furthermore, the relatively small sample size may have resulted in insufficient statistical power to detect differences between observed morphine and M3G concentrations in relation to NRS.

Conclusions

In frail older cardiac surgery patients, morphine glucuronidation is similar compared to general ICU patients, while elimination of morphine through other routes is decreased and M3G elimination is increased. Analgesic response to standardized morphine treatment varied substantially and was only satisfactory in a minority of patients. Personalized pain management is essential for older patients to ensure safe and efficient postoperative pain relief.

ACKNOWLEDGEMENTS

None

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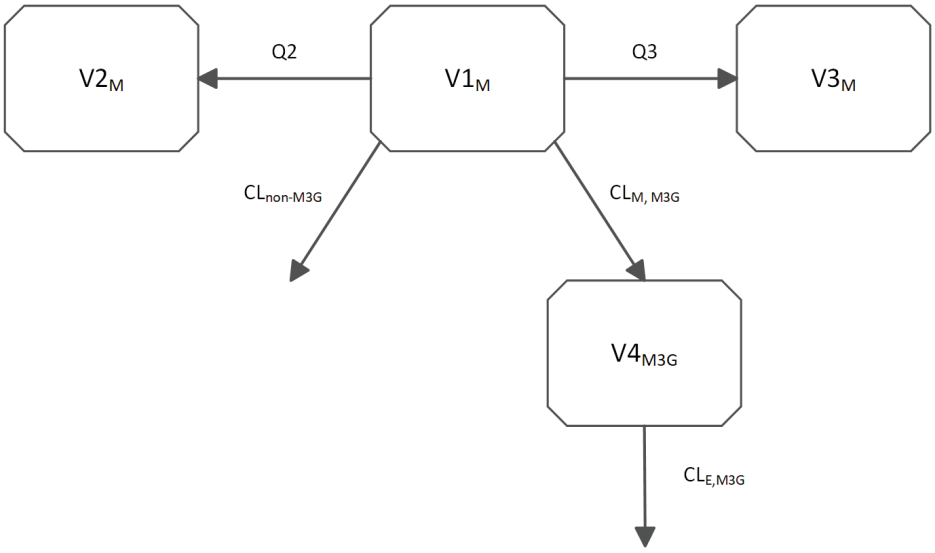
SUPPLEMENTARY MATERIAL

Supplementary table 1. Parameter estimates of the population pharmacokinetic original ICU model (consisting of postcardiac surgery and critically ill patients) and optimized model of morphine and M3G in frail elderly cardiac surgery patients

Fixed effects	Model of Ahlers et al.[14]	Deviating estimates for frail elderly
Morphine		
$V1_M$ (L)	17.1	-
$V2_M$ (L)	88.6	-
$V3_M$ (L)	399	-
Q_2 (L/min)	1.33	-
Q_3 (L/min)	0.156	-
$CL_{non\text{-}M3G}$ (L/min)	0.539	0.333 (RSE 13.6%)
M3G formation ($CL_{m,M3G}$) (L/min)	0.573	-
M3G		
$V4_{M3G}$ (L)	23 (fixed)	-
M3G elimination ($CL_{e,M3G}$) (L/min)	0.0423	0.0605 (RSE 6.4%)

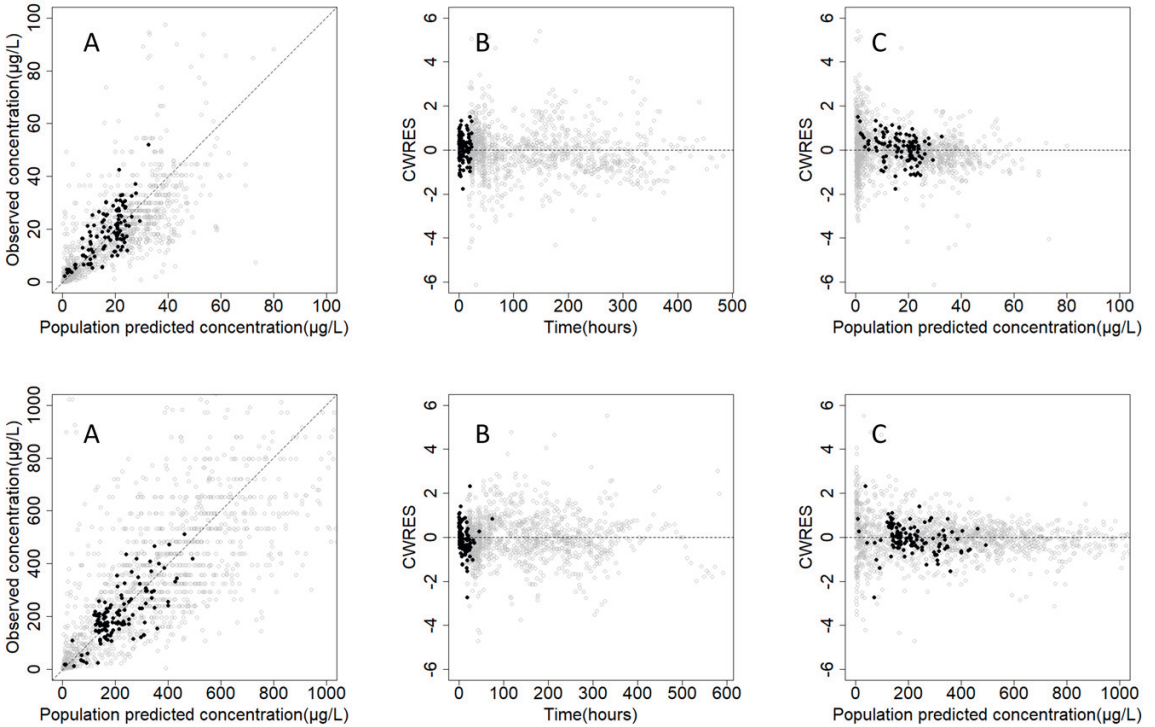
ICU = intensive care unit; M = morphine; M3G = morphine-3-glucuronide; V1 and V4 = central volumes of distribution for morphine and M3G, respectively, V2 and V3 = peripheral compartments; Q_2 and Q_3 = inter-compartmental clearances for morphine. $CL_{non\text{-}M3G}$ = morphine clearance through other routes with creatinine concentration of 80 µmol/L; $CL_{m,M3G}$ = M3G formation; $CL_{e,M3G}$ = M3G elimination; - = unchanged compared to Model of Ahlers et al.

Supplementary figure 1. Schematic representation of the population pharmacokinetic structural model of morphine and M3G.



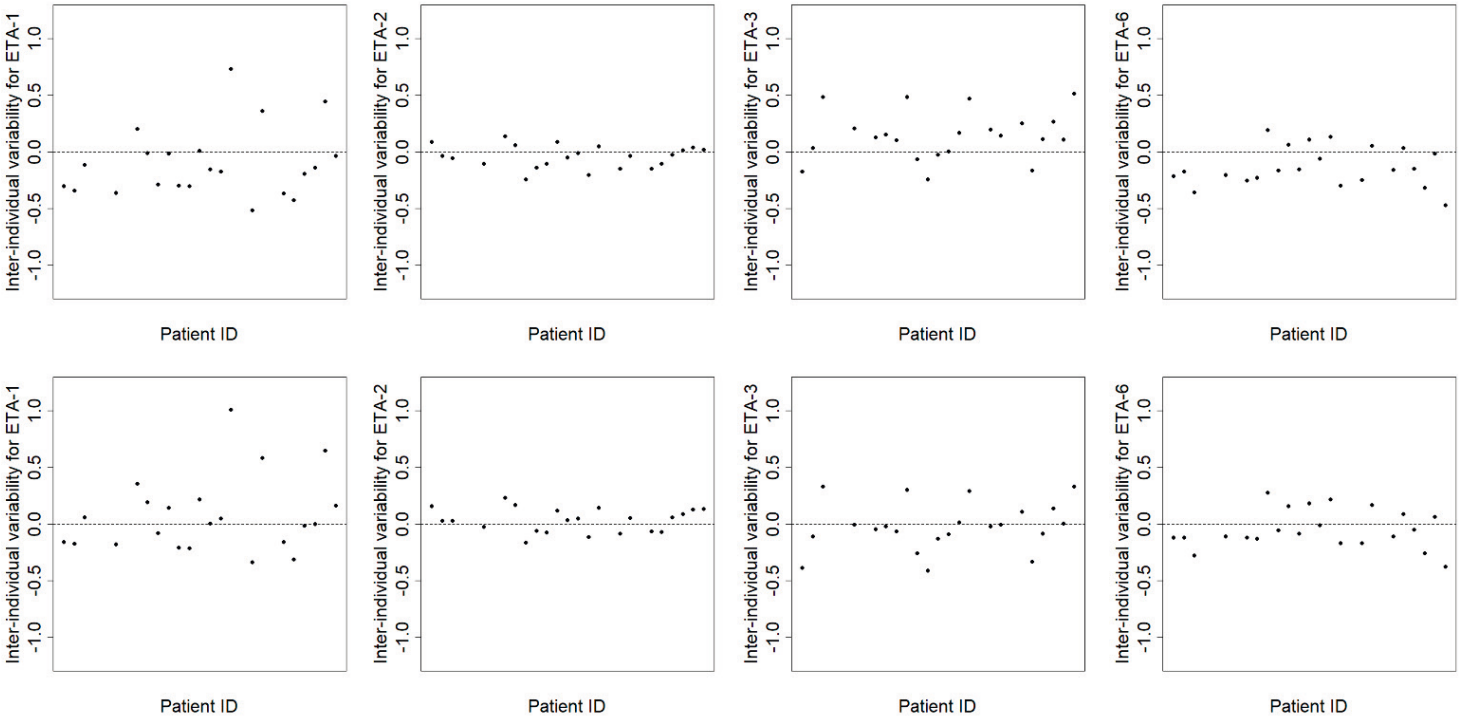
The dose is administered in the central compartment ($V1_M$).
M = morphine; M3G = morphine-3-glucuronide; $V1_M$ and $V4_{M3G}$ = central volumes of distribution of morphine and M3G, respectively; $V2_M$ and $V3_M$ = peripheral volume of distribution of morphine; Q1 and Q2 = inter-compartmental clearances for morphine. $CL_{non\text{-}M3G}$ = morphine clearance through other routes; $CL_{m,M3G}$ = M3G formation clearance; $CL_{e,M3G}$ = M3G elimination clearance.

Supplementary figure 2. Goodness-of-fit plots obtained in a Bayesian re-estimation (i.e., MAXEVAL = 0 fit) with the original model for general ICU patients.



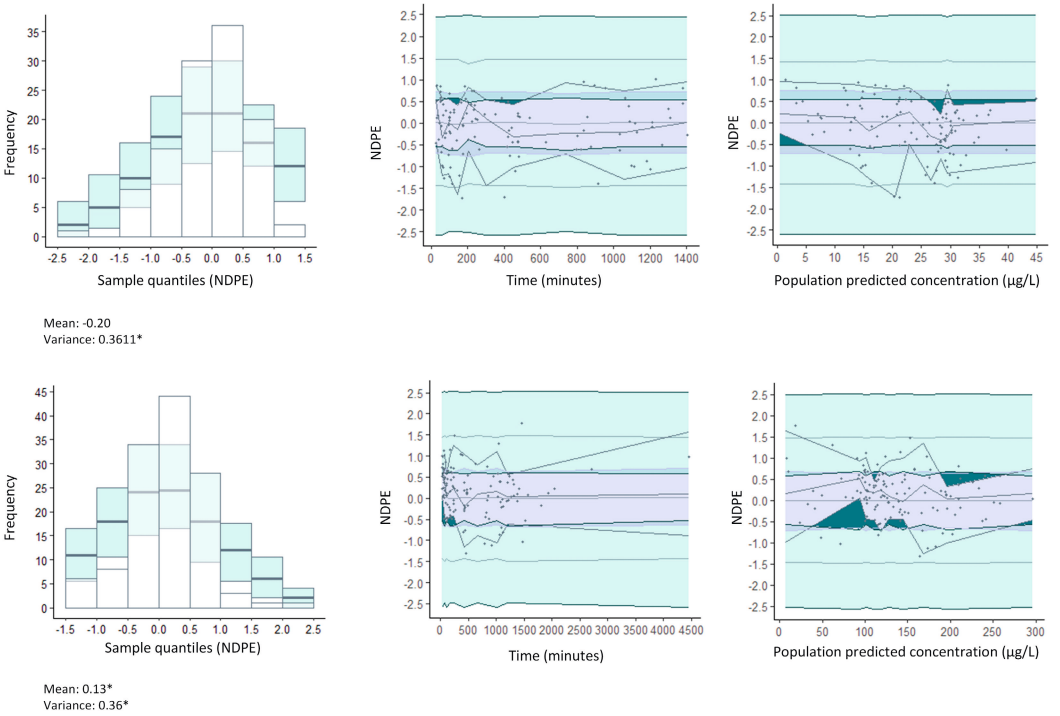
(A) Observed concentration versus population predicted concentration. The dotted line indicates the line of unity. (B) Conditional weighted residuals (CWRES) versus time. (C) CWRES versus population predicted concentration. Top row represents morphine, bottom row morphine-3-glucuronide. The black dots represent the frail elderly patients, the grey symbols represents the general ICU population (i.e., post cardiac surgery and critically ill patients).

Supplementary figure 3. Individual deviations from typical parameter values (eta-values) plotted for the Bayesian reestimation (i.e., MAXEVAL = 0 fit) (top row) and optimized PK model for frail elderly patients (bottom row).



From left to right: ETA-1 = $CL_{non\text{-}M3G}$, morphine clearance through other routes; ETA-2 = $CL_{m,M3G}$, M3G formation clearance; ETA-3 = $CL_{e,M3G,}$ M3G elimination clearance; ETA-6 = $V2_{M3G}$, central volume of distribution of M3G. M3G = morphine-3-glucuronide.

Supplementary figure 4. Results of the normalized prediction distribution error (NDPE) analysis with the final PK model for morphine (top) and M3G (bottom) in frail elderly after cardiac surgery.



*The histogram shows the NDPE frequency distribution. The green bars indicate a normal distribution. The values for the mean and variance of the NPDE distribution are given below each histogram with * indicating a statistically significant difference of a mean of 0 and a variance of 1 at $p < 0.05$ level as determined by the Student's t-test and the Fisher test of variance. The distribution of NDPE versus time after first dose and NDPE vs. exponent of the concentration are also shown. Symbols represent NPDE values of each observation, the lines represent the 2.5th, 50th, and 97.5th percentile of the observations and the 95% prediction intervals of these percentiles in the simulated data are represented by the shaded areas.*

Chapter 7

General discussion

GENERAL DISCUSSION

Cardiac surgery in elderly patients aims to improve functional capacity and overall survival, but may also precipitate major morbidity and mortality.[1–3] The rising complexity of cardiac patients with high surgical risk necessitates different treatment approaches. Existing guidelines, reliant on scores like EuroSCORE II, often overlook crucial factors such as frailty, leading to suboptimal decision-making. Additionally, treatment guidelines primarily prioritize reducing adverse events, such as mortality, rather than focusing on symptom relief or improvements in quality of life and daily functioning. Particularly in frail elderly, the benefits of surgery may be uncertain. For those patients, a multidisciplinary patient-centered approach to find consensus for individualized treatment and prehabilitation have shown to improve perioperative outcomes, disability, quality of life and recovery.[4–7] However, the complexity of frail cardiac patients extends beyond the preoperative period. The ageing population presents unique postoperative challenges, including higher susceptibility to adverse drug events, more pain and prolonged recovery times.[4,5] Also, nearly half of all adverse events in hospitalized patients arise in the early postoperative recovery phase at the general ward.[8–10] Advanced monitoring techniques, including non-invasive continuous monitoring, provide valuable insights into the patient's physiological status during the postoperative period, allowing for timely interventions to prevent adverse outcomes. In addition, when selecting and dosing medications to treat postoperative pain in elderly patients, careful considerations are necessitated due to age-related changes in pharmacokinetics and pharmacodynamics.[11] Therefore, personalized medication and pain management strategies are essential integral components of perioperative care for older patients. As frail elderly are at increased risk of postoperative complications and the majority of complications occur at the general ward, these patients may benefit of intensive monitoring and personalized pain management strategies in the early postoperative phase. This thesis studied novel risk factors for postoperative complications and poor functional outcome using systematic analysis of continuous monitoring data and pharmacokinetic models collected in a high-risk surgery population. In this chapter the findings of the studies presented in this thesis are summarized and discussed.

Unraveling the risk of polypharmacy in frail older patients preceding surgery

Older patients with polypharmacy represent a high-risk group of the perioperative population, due to decreased postoperative survival, increased adverse event rates, and higher health resource utilization.[6] Also, older patients are at increased risk for worse quality of life after surgery.[12–14] To improve risk stratification and facilitate targeted prehabilitation, clinicians perform frailty assessments.[2,15] However, frailty

assessments are time consuming, thus the preference leans towards a simple, yet effective test capable of providing insights into postoperative outcomes. Routine preoperative screening procedures include evaluations of patients' medication regimen, with polypharmacy serving as valuable indicator for estimating operative risk and predicting poor functional outcomes and recovery.[4] In **chapter 2**, we studied polypharmacy as individual risk factor for postoperative functional decline in frail elderly and assessed which commonly used drugs were associated with adverse outcome. Polypharmacy is often defined as the use of 5 or more different drugs by one individual and excessive polypharmacy as the use of 10 or more. In The Netherlands, approximately 45% of patients aged 65 years and older have polypharmacy and almost 20% of patients aged 75 years and older have excessive polypharmacy to treat underlying disease.[16] In addition, polypharmacy exacerbates the risk of adverse drug-drug interactions, especially in the perioperative setting, due to the introduction of unfamiliar anesthetic and analgesic drugs during this period, which will increase the potential for unintended pharmacological interactions. Furthermore, acute changes in end-organ function, a frequent occurrence in the perioperative setting, may further disrupt drug metabolism, exacerbating the risk of adverse outcomes.[16] In our study, we found that polypharmacy is associated with functional decline one year after cardiac surgery. Patients with excessive polypharmacy had almost twice the incidence of functional decline compared to patients without polypharmacy. In addition, patients using specific types of medication such as benzodiazepines, antidepressants and proton pomp inhibiters were at higher risk to develop functional decline. Several studies have examined ways for deprescribing to improve outcomes and refer to consensus lists such as the STOPP criteria.[17,18] These criteria help to identify inappropriate medications in older adults, focusing on risks like drug-drug interactions and high dosages. The aforementioned type of medications are commonly used medications on this list and may be temporarily discontinued upon evaluation by the treating physician in order to improve postoperative outcome. In **chapter 3**, we addressed the association between frailty domains and chronic pain following cardiac surgery. In this study we confirmed our previous results and found that patients with excessive polypharmacy belonged to a high-risk population with increased risks to develop chronic pain. Also, chronic pain led to worse quality of life, which was very common in frail elderly following cardiac surgery. The results of these studies advocate that early identification of specific risk factors may be used to identify older patients at risk for adverse postoperative outcome. In addition, as a medication review is part of routine perioperative screening, we suggest using it as a screening tool to identify high-risk cardiac surgery patients who may benefit from further frailty assessment. This acknowledges the relationship between frailty and the use of multiple medication to treat underlying morbidities.[19]

Essential vital signs to consider for continuous monitoring at the general ward

Failure to rescue is defined as the number of deaths in patients who develop postoperative complications, a metric recommended by the National Quality Forum to enhance healthcare quality and patient safety. The failure in timely recognizing patient deterioration and provide appropriate care at the general ward contributes to both failure to rescue and delayed escalation of care.[20–22] Ironically, the general ward is traditionally regarded as a place of recovery for the more stable patients, in transition to leave the hospital. Several studies demonstrated that there are clear signs of patient deterioration hours before events such as cardiopulmonary or respiratory arrest.[23] Over the last years, it was suggested that automated noninvasive continuous ward monitoring would be a promising approach to closely follow changes in vital signs to identify patients at the earliest signs of deterioration for timely intervention, but evidence in high-risk surgical patients is still limited.[24–26] In **chapter 4**, we evaluated if clinical deterioration was preceded by significant changes in vital signs in frail elderly patients following cardiac surgery, using continuous monitoring at the general ward. We found that clinical deterioration was preceded by more severe abnormal respiratory rates, but not by differences in heart rate or oxygen saturation. Respiratory rate has earlier been identified as the most accurate vital sign for predicting serious adverse events such as cardiac arrests in general ward patients and abnormal respiration has previously been associated with an almost doubled risk of in-hospital mortality.[27–29] Additionally, an increased respiratory rate has been a known predictor of early clinical deterioration after discharge from the emergency department.[30] In frail elderly following cardiac surgery in our study, RR was abnormal 70% of the time of MEWS measurements and the severity of an abnormal RR was significantly associated with clinical deterioration. Given the suboptimal assessment of respiratory rate in clinical settings, we would advise the use of continuous respiratory rate monitoring in high-risk patients on general wards as it can improve quality of care and patient outcome. In **chapter 5**, we reported that 80% of frail elderly patients experience hypoxemia after ICU discharge following cardiac surgery. Hypoxemia is a known risk factor for adverse outcomes, such as myocardial ischemia and respiratory failure.[31] Nevertheless, SpO_2 levels measured with spot check monitoring by nurses seriously underestimate the incidence and severity of hypoxemia.[32,33] , Also, it is important to keep in mind that frail elderly patients following cardiac surgery often require oxygen suppletion therapy at the general ward, thereby potentially (partly) restoring SpO_2 levels in patients with underlying hypoxemia. In our study population, 77% of the frail elderly patients required a suppletion of >5L O_2. Given the high percentage of hypoxemia and the need for oxygen suppletion in this high-risk population, it raises the question whether measuring saturation adds value to the early detection of clinical deterioration. In our

opinion, measuring oxygen saturation is indeed important following cardiac surgery, as oxygen saturation levels measured with spot check monitoring by nurses seriously underestimate the incidence and severity of hypoxemia, but it may not aid in the early detection of deteriorating patients. Regarding heart rate, post cardiac surgery patients frequently exhibit arrhythmia. Unfortunately, our monitoring system was unable to capture irregular heart rate. Yet, these arrhythmias were all captured with regular sport check monitoring by nurses and intervention was often unnecessary as the arrhythmias typically resolved spontaneously. The continuous measurement of heart rate in our opinion, may therefore not significantly enhance the early detection of clinical deterioration. Instead, respiratory rate appears to be a more reliable indicator.

Optimizing postoperative medication management in the frail elderly patient

Postoperative treatment with opioids and benzodiazepines is common during recovery from cardiac surgery. Yet, the frequent use of these high risk medications raises concerns among healthcare providers regarding the fear of overdosing in frail elderly patients. Respiratory depression (i.e., hypoxemia or the need for oxygen suppletion) due to overdosing is the most adverse effect of high risk medication during postoperative recovery.[31,32,34–36] Additionally, different clinical studies demonstrated that opioid therapy is often associated with excessive respiratory depression in patients aged 60 years or older.[37] In our study population, frail elderly patients receiving high risk medication at the general ward following cardiac surgery demonstrated more hypoxemic episodes than patients without high risk medication (**chapter 5**). However, the period of maximum treatment effect (including the Tmax of each drug) was not associated with an increased risk of recurrent hypoxemia. Yet, prescription of these high risk medication, for example opioid therapy in the elderly, is often associated with adverse effects such as excessive respiratory depression and challenges surrounding prescriptions.[5,37] Still, it seems common practice to use adult protocols in elderly patients. However, older patient populations are more heterogeneous in terms of physiology and morbidity, resulting in a different response to medications.[5] This heterogeneity is even more pronounced in frail patients, but its effects on pharmacokinetics and pharmacodynamics are poorly studied.[38,39] In **chapter 6** we evaluated the pharmacokinetics and analgesic response of morphine and its metabolite M3G in frail elderly patients. We demonstrated that frail elderly did not show differences in morphine glucuronidation, while elimination of morphine through other routes was decreased and M3G elimination increased. These PK differences in frail elderly compared to the ICU population resulted in a 20% difference in steady-state concentration after morphine infusion. Also, standardized pain management with morphine resulted in substantial variation in analgesic response in frail elderly,

including oversedation and severe pain. Clearly, the effects of age and frailty on the pharmacokinetics of morphine do not fully explain the observation that frail elderly patients are more sensitive to the therapeutic and adverse effects of opioids. Therefore, dose adjustments and careful monitoring are essential requirements when administering these types of high risk medication.

How to be aware in frail elderly patients?

In conclusion, the perioperative management of the frail elderly patient is a complex puzzle among preoperative risk factors, perioperative (pain) medication management, and postoperative monitoring to prevent complications. The high inter-individual variation in all this factors enhances the importance of risk stratification, individualized perioperative treatment and close monitoring in the frail elderly patient. In this thesis we studied novel risk factors for postoperative complications and poor functional outcome in a high-risk surgical population and came to the following recommendations. At first, during preoperative assessment of the older cardiac surgery patient, polypharmacy should be given prominent consideration, due to its dual significance: it is a risk factor for the development of postoperative functional decline and a target for potential prevention of complications through preoperative assessment of the patients' medication, using the STOPP criteria. Second, it is essential to ensure close monitoring at the general ward, as the early postoperative period carries a heightened risk of complications, especially in frail elderly. The use of continuous monitoring for respiratory rate in frail elderly patients might be useful in the early detection of clinical deterioration. Lastly, as chronic pain is associated with adverse outcomes, it is important to establish effective pain management. This should involve personalized care, which can be provided without concern for adverse effects, as they are not associated with the administration of high risk medication in frail elderly patients.

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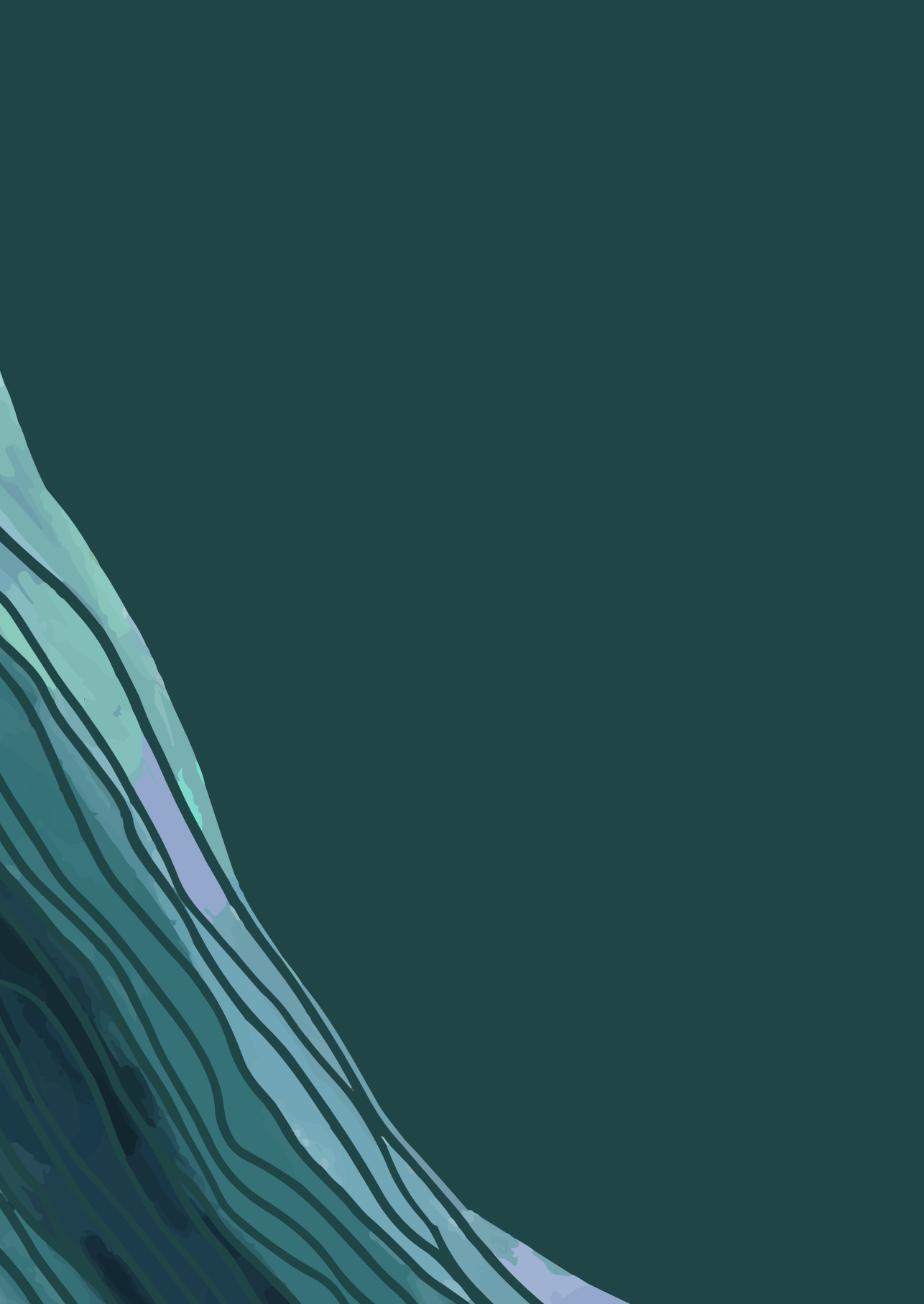


Appendix

English summary

ENGLISH SUMMARY

Population ageing and healthcare innovations have led to an increased number of elderly patients undergoing cardiac surgery. Longevity is associated with a higher risk of chronic diseases, polypharmacy and frailty. Particularly, frail elderly patients face an increased risk of postoperative complications and are consequently more susceptible for disability and dependent living. If not addressed carefully, longevity may come at the expense of self-reliance and overall quality of life. The aim of this thesis is to evaluate novel risk factors for postoperative complications and poor functional outcomes using systematic analysis of continuous monitoring data and pharmacokinetic models collected in a high-risk surgical population.

Chapter 2 and **chapter 3** focus on the relationship between frailty and functional outcome after cardiac surgery in a retrospective cohort of frail elderly patients. Since the population ages and the number of elderly requiring cardiac surgery is rising, identifying preoperative risk factors becomes more important in an attempt to reduce adverse functional outcome. **Chapter 2** evaluates the association between preoperative medication use and functional decline in elderly cardiac surgery patients and compares polypharmacy as a preoperative screening tool to a clinical frailty assessment. Polypharmacy was associated with functional decline, defined as a worse health related quality of life or disability one year after surgery (aRRs 1.57, 95% CI 1.23 – 1.98). Additionally, a model including polypharmacy improved preoperative risk classification (NRI: 17%, 95% CI 0.06 – 0.27). Meaning, one in five patients was correctly reclassified to a different risk category after stratification based on polypharmacy, compared to the basic model with age, sex and type of surgery alone. Specifically cardiovascular medication, proton pomp inhibitors and central nervous system medication demonstrated higher risk for postoperative functional decline. This chapter emphasizes the potential of using a medication review as a simple and useful tool to identify elderly patients at risk for postoperative adverse outcomes following cardiac surgery. **Chapter 3** of this thesis assesses which frailty domains are associated with chronic pain after cardiac surgery in older patients. Although a preoperative assessment routinely includes risk stratification for cardiac or pulmonary complications, standardized screening for the risk to develop chronic pain is less common. Given the negative effects on postoperative outcome, it is essential that risk factors for chronic pain after surgery are identified in order to initiate preventive strategies. Pain was evaluated with the Short-Form 36 questionnaire prior to and one year after surgery. Chronic pain after cardiac surgery was reported in 182 out of 518 patients (35%). Medication use, living alone, poor mobility, physical functioning and preoperative HRQL (health related quality of life) were associated with chronic pain

after surgery. Patients with chronic pain after surgery experienced worse physical HRQL compared to patients without chronic pain (β 10.37, 99% CI −12.57 – −8.17). The results of chapter 2 and 3 advocate that preoperative frailty assessment may be used to identify older patients at risk for adverse postoperative functional outcomes, including chronic pain and disability.

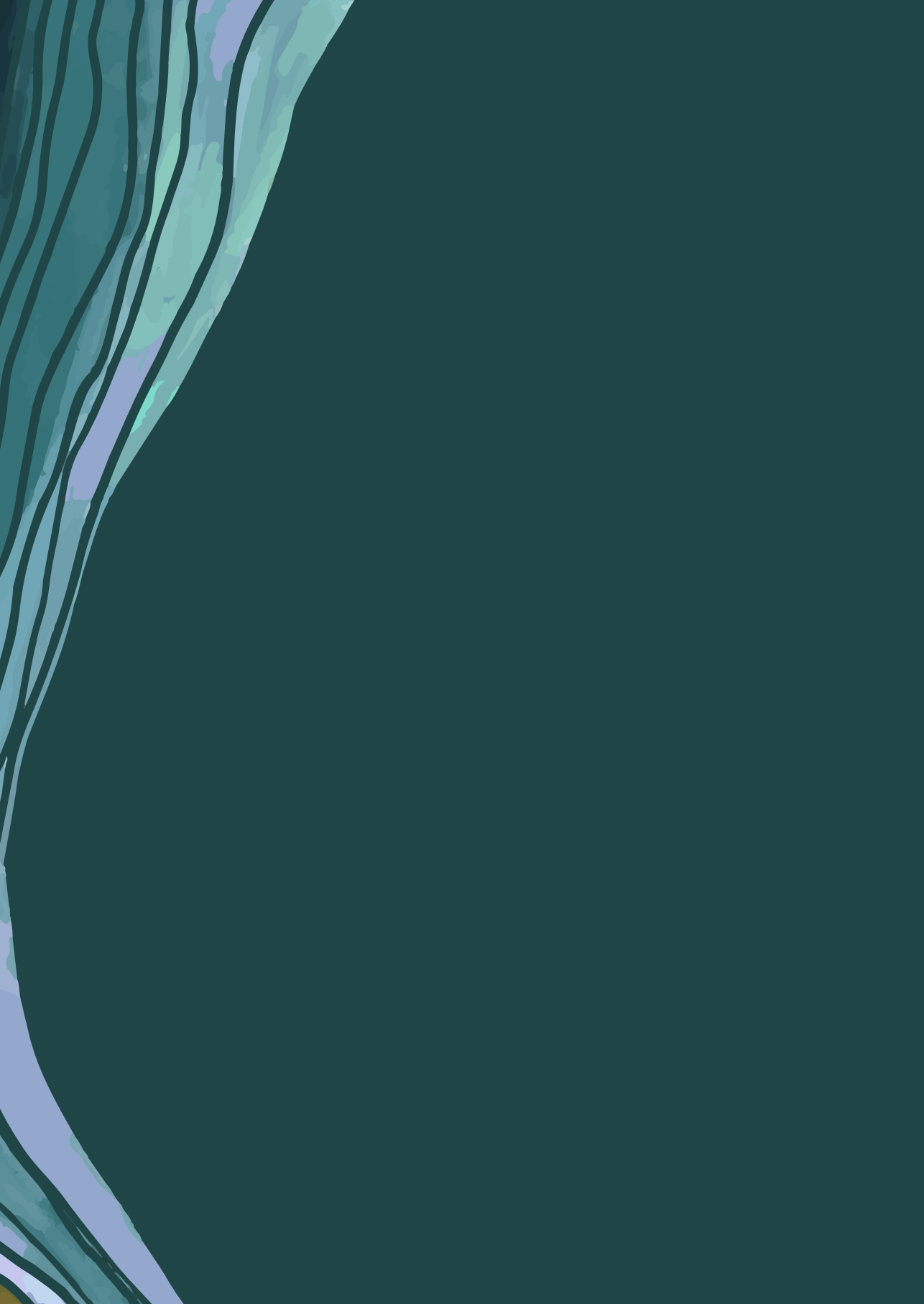
Chapter 4 and **chapter 5** prospectively study continuous monitoring of vital signs after ICU discharge in relation to clinical deterioration and side effects of high risk medication (HRM) in frail elderly patients following cardiac surgery. In recent years, wireless devices capable of continuously monitoring of heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO_2) have become available, which can detect clinical deterioration. **Chapter 4** analyses continuous vital signs before clinical deterioration in frail cardiac surgery patients at the general ward. The primary endpoint was clinical deterioration, defined as modified Early Warning Score (MEWS) ≥ 5. HR, RR and SpO_2 were continuously monitored for 72 hours at the general ward. Predefined thresholds were used to define abnormal HR, RR and SpO_2 during 4 hours before clinical deterioration and compared with controls. The duration and severity of abnormal vital signs were calculated to examine the association with clinical deterioration. A total of 70 patients was included in this study, of which 22 experienced clinical deterioration (31%). RR was abnormal during 70% of the time, but not different between groups (71% vs. 68%, P=0.60). Additionally, the severity of abnormal RR was associated with clinical deterioration (OR 2.54, 95% CI 1.05 – 6.47). Furthermore, among patients with clinical deterioration, oxygen use >5L O_2/min and arrhythmia were more common (77% vs. 54% among controls, P<0.001 and 31% vs. 11% of controls, P<0.01, respectively). However, abnormal continuous SpO_2 and HR measurements were not associated with clinical deterioration. As elderly patients often experience abnormal respiratory rates following cardiac surgery, continuous RR monitoring may be useful in an attempt to reduce failure to rescue rates. Before implementation adequately powered randomized controlled trials are needed to demonstrate its effectiveness in preventing clinical deterioration and adverse outcomes. **Chapter 5** describes the effects of opioids and benzodiazepines (i.e., HRM) on postoperative hypoxemia in frail elderly cardiac surgery patients, using continuous monitoring at the general ward. Opioids and benzodiazepines are widely used to treat postoperative pain and anxiety at the general ward, but older patients are more susceptible for the depressant effects. The primary endpoint of this study was hypoxemia, defined as SpO_2 <90% for ≥10 minutes. HRM were administered to 51/71 (73%) patients. Postoperative hypoxemia occurred in 56 (80%) patients. During the period of maximum treatment effect HRM was not associated with recurrent hypoxemia (aRR 1.21, 95% CI 0.74 – 2.01, P=0.47). However, patients with HRM had more hypoxemic episodes (336 versus 126 for patients without

HRM, P <0.001) and spent more time below abnormal SpO_2 thresholds. Therefore, careful monitoring is essential when using HRM for pain and anxiety in frail elderly patients.

As postoperative pain following cardiac surgery is common and still poorly managed, we aimed to identify strategies for safer medication use in the frail elderly population. In **chapter 6** we report the prospective analysis of the pharmacokinetics and analgesic response of morphine treatment in frail older cardiac surgery patients following cardiac surgery. We used a previously published model to explore differences in PK in frail elderly patients compared to general ICU patients. To study the analgesic response, clinically driven dose adjustments were analysed in conjunction with corresponding individual morphine and M3G concentrations, postoperative severe pain and oversedation in the frail elderly population. In total, 252 morphine and M3G concentrations were obtained from 22 frail elderly patients after cardiac surgery.

Morphine glucuronidation remained unchanged, whereas for morphine clearance through other routes frail elderly patients showed a 39% decrease and for M3G elimination a 43% increase compared to ICU patients. Overall, this had minimal impact on concentration-time profiles with bolus doses, while for continuous infusion this resulted in a 20% difference in steady-state concentration. Additionally, an adequate analgesic response was observed in only 18%, with 82% experiencing oversedation and 50% experiencing severe pain. Standardized pain management with morphine thus resulted in substantial variation in analgesic response. However, no significant correlation was found between the relation of morphine or M3G concentrations and NRS scores. To explore the exposure, efficacy and safety of morphine dosing when initiating opioid therapy in frail elderly patients, PKPD simulations with different dosing intervals need to be evaluated in future clinical trials.

In summary, this thesis gives perspectives concerning perioperative management of frail elderly cardiac surgery patients. To place the findings of the research presented in this thesis in a wider context, **chapter 7** provides a reflection on our results and overall conclusions and offers recommendations for clinical care and further research.



Appendix

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Innovaties in de gezondheidszorg en de toenemende gemiddelde leeftijd van de bevolking leidt tot een groter aantal oudere patiënten dat een hartoperatie ondergaat. Oudere leeftijd is geassocieerd met een hoger risico op chronische ziekten, polyfarmacie en kwetsbaarheid. Met name kwetsbare oudere patiënten lopen een verhoogd risico op complicaties en postoperatieve invaliditeit. Hierdoor kan een langere levensduur ten koste gaan van zelfredzaamheid en kwaliteit van leven. Het doel van dit proefschrift was om nieuwe risicofactoren voor postoperatieve complicaties en ongunstige functionele uitkomsten te evalueren met behulp van een systematische analyse van data verzameld met continue monitoring en farmacokinetische modellen in een chirurgische hoog risico populatie.

Hoofdstuk 2 en hoofdstuk 3 richten zich op de relatie tussen kwetsbaarheid en functionele uitkomst na hartchirurgie in een retrospectief cohort van kwetsbare oudere patiënten. Gezien het feit dat de bevolking veroudert en het aantal ouderen dat hartchirurgie nodig heeft toeneemt, wordt het identificeren van preoperatieve risicofactoren belangrijker in een poging om ongunstige functionele uitkomsten te verminderen. **Hoofdstuk 2** onderzoekt de associatie tussen het gebruik van preoperatieve medicatie en functionele achteruitgang bij oudere patiënten die hartchirurgie ondergaan en vergelijkt polyfarmacie als een preoperatief screeningsinstrument met een uitgebreide klinische kwetsbaarheidsbeoordeling. Polyfarmacie bleek geassocieerd te zijn met functionele achteruitgang, gedefinieerd als een slechtere kwaliteit van leven of invaliditeit een jaar na de operatie (aRR 1.57, 95% CI 1.23 – 1.98). Bovendien verbeterde een model met polyfarmacie de preoperatieve risicoclassificatie (NRI: 17%, 95% CI 0.06 – 0.27). Dit hoofdstuk benadrukt het potentieel van het gebruik van een medicatiebeoordeling als een eenvoudig en nuttig instrument om oudere patiënten met een verhoogd risico op postoperatieve ongunstige uitkomsten na hartchirurgie al preoperatief te identificeren. **Hoofdstuk 3** van dit proefschrift evalueert welke kwetsbaarheidsdomeinen geassocieerd zijn met chronische pijn na hartchirurgie in oudere patiënten. Hoewel een preoperatieve beoordeling routinematig risicostratificatie voor hart- of longcomplicaties omvat, is gestandaardiseerd screenen op het risico om chronische pijn te ontwikkelen na de operatie minder gebruikelijk. Gezien de negatieve effecten van pijn op postoperatieve uitkomsten en functioneren is het essentieel dat risicofactoren voor postoperatieve pijn worden geïdentificeerd om preventieve strategieën te initiëren. Pijn werd beoordeeld vóór en één jaar na de operatie met behulp van de Short-Form 36 vragenlijst. Chronische pijn na hartchirurgie werd gemeld bij 182 van de 518 kwetsbare oudere patiënten (35%). De volgende risicofactoren waren geassocieerd met postoperatieve chronische pijn:

medicatiegebruik, alleenwonend, verminderde mobiliteit, verminderde lichamelijke functie en verminderde preoperatieve HRQL (gezondheidsgerelateerde kwaliteit van leven). Patiënten mét postoperatieve chronische pijn bleken een slechtere fysieke HRQL te hebben in vergelijking met patiënten zónder chronische pijn (β 10.37, 99% CI −12.57 – −8.17). De resultaten van hoofdstuk 2 en 3 pleiten ervoor dat een preoperatieve screening op specifieke kwetsbaarheidsparameters kan worden gebruikt om oudere patiënten te identificeren die een verhoogd risico lopen op ongunstige postoperatieve functionele uitkomsten, waaronder chronische pijn.

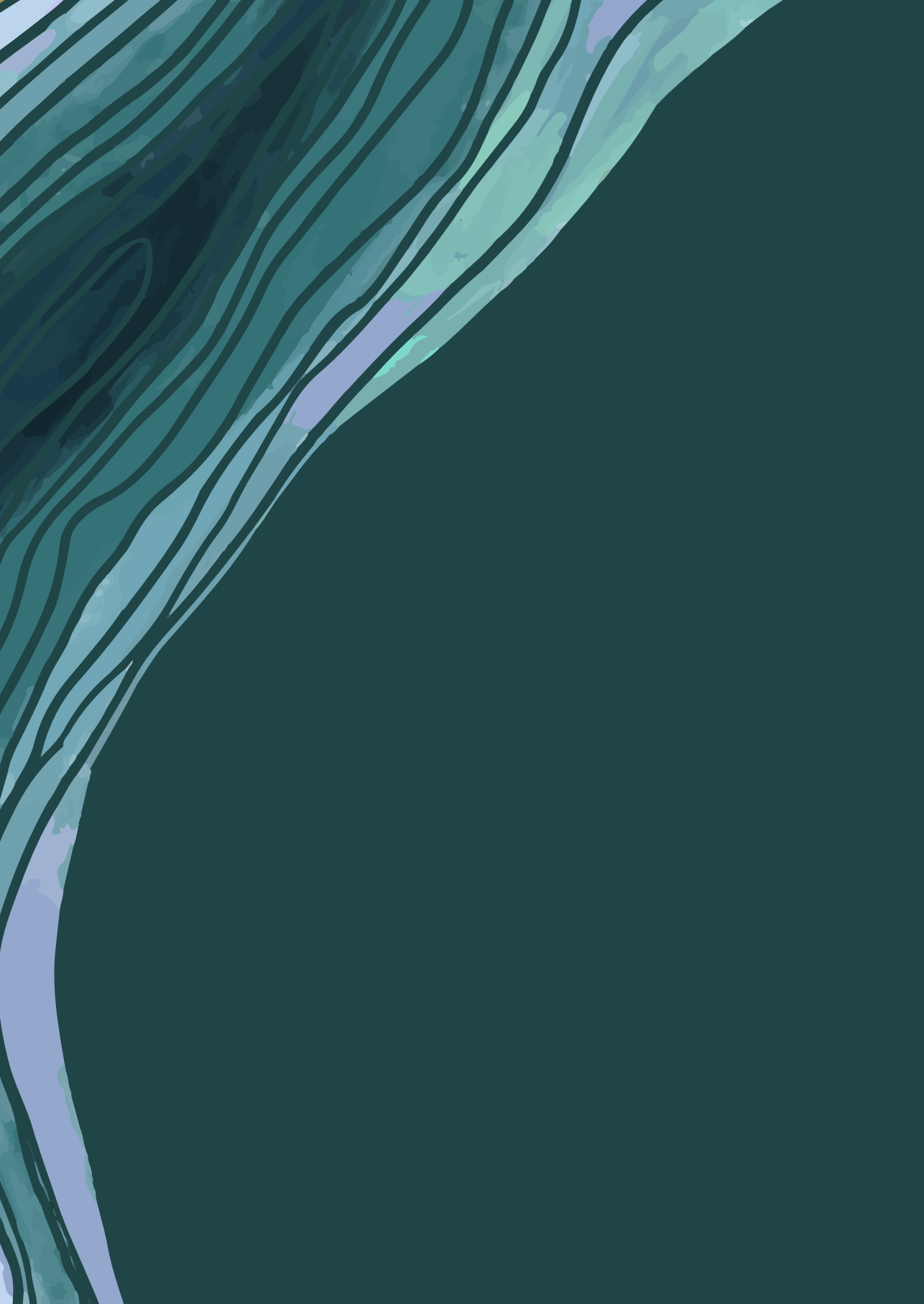
Voor de analyses van **hoofdstuk 4 en hoofdstuk 5** is een prospectieve studie opgezet waarbij trends in vitale functies na ontslag van de intensive care werden geanalyseerd in relatie tot het optreden van klinische verslechtering en bijwerkingen van medicatie met een hoog risico medicament (HRM) in kwetsbare oudere patiënten na hartchirurgie. De afgelopen jaren zijn draadloze apparaten beschikbaar gekomen die continu hartslag (HR), ademhalingsfrequentie (RR) en zuurstofsaturatie (SpO_2) kunnen monitoren. **Hoofdstuk 4** analyseert de continue HR, RR en SpO_2 data voorafgaand aan klinische verslechtering bij kwetsbare hartchirurgische patiënten in de vroege postoperatieve fase op de verpleegafdeling. Het primaire eindpunt was klinische verslechtering, gedefinieerd als een Modified Early Warning Score (MEWS) ≥ 5 gemeten door de verpleegkundige. HR, RR en SpO_2 werden continu gemonitord gedurende 72 uur. Vooraf bepaalde drempels werden gebruikt om abnormale HR, RR en SpO_2 te definiëren in de 4 uur voorafgaand aan klinische verslechtering en deze data werd vergeleken met controle patiënten (zonder klinische verslechtering). De duur en ernst van de afwijkende vitale functies werd bepaald om de associatie met klinische verslechtering te onderzoeken. In totaal namen 70 patiënten deel aan dit onderzoek, waarvan er in 22 patiënten klinische verslechtering optrad (31%). RR was gedurende 70% van de tijd abnormaal, maar niet verschillend tussen patiënten mét en zónder klinische verslechtering (71% vs. 68%, P=0.60). De ernst van een abnormale RR was wel geassocieerd met klinische verslechtering (OR 2.54, 95% CI 1.05 – 6.47). Hiernaast kwamen bij patiënten met klinische verslechtering het gebruik van zuurstof >5L O_2/min en hartritmestoornissen gediagnosticeerd door de verpleegkundige vaker voor (77% vs. 54% bij controles, P<0.001 en 31% vs. 11% bij controles, P<0.01, respectievelijk). Afwijkingen in SpO_2 en HR met behulp van continue monitoring waren echter niet geassocieerd met klinische verslechtering. Gezien oudere patiënten vaak afwijkingen vertonen in ademhalingsfrequentie na hartchirurgie, kan continue RR-bewaking nuttig zijn om klinische verslechtering vroegtijdig op te sporen. Voordat implementatie plaatsvindt, zijn echter voldoende grote gerandomiseerde onderzoeken nodig om de effectiviteit ervan bij het voorkomen van klinische verslechtering en ongunstige uitkomsten aan te tonen. **Hoofdstuk 5** beschrijft de effecten van

opioïden en benzodiazepinen, d.w.z. hoog risico medicatie (HRM) op postoperatieve hypoxemie bij kwetsbare oudere hartchirurgiepatiënten. Opioïden en benzodiazepinen worden veel gebruikt om postoperatieve pijn en angst op de algemene afdeling te behandelen, maar oudere patiënten zijn vaak gevoeliger voor de depressieve effecten op ademhaling en saturatie. Het primaire eindpunt van dit onderzoek was hypoxemie, gedefinieerd als SpO_2 <90% gedurende ≥10 minuten. HRM werden toegediend aan 51/71 (73%) patiënten en postoperatieve hypoxemie trad op bij 56 (80%) patiënten. In de periode vanaf de gift van het geneesmiddel tot aan de gemiddelde tijd die het geneesmiddel nodig heeft om de maximale plasmaconcentratie te bereiken (Tmax) trad hypoxemie niet vaker op (aRR 1.21, 95% CI 0.74 – 2.01, P=0.47). Echter, bleken patiënten met HRM wel vaker een episode van hypoxemie te ervaren (336 versus 126 voor patiënten zonder HRM, P <0.001) en brachten zij meer tijd door met abnormale SpO_2-levels. Zorgvuldige monitoring is daarom essentieel bij het gebruik van HRM voor pijn en angst bij kwetsbare oudere patiënten in de vroege postoperatieve fase.

Gezien postoperatieve pijn nog vaak voorkomt en nog niet optimaal behandeld wordt door onder andere de angst bij zorgpersoneel voor overdosering met opiaten, hebben we geprobeerd strategieën te identificeren voor veiliger medicijngebruik. In **hoofdstuk 6** rapporteren we de prospectieve analyse van de farmacokinetiek (PK) en de analgetische respons van morfinebehandeling bij kwetsbare oudere patiënten na hartchirurgie. We hebben een eerder gepubliceerd model gebruikt om verschillen in PK te onderzoeken bij kwetsbare oudere patiënten in vergelijking met algemene intensive care (IC)-patiënten. Om de analgetische respons te bestuderen, werden postoperatief klinisch gestuurde dosisaanpassingen, morfine- en M3G-concentraties en bijwerkingen van morfinebehandeling geanalyseerd in de kwetsbare oudere populatie. In totaal werden 252 morfine- en M3G-concentraties verkregen van 22 kwetsbare oudere patiënten na hartchirurgie. Morfine glucuronidatie bleef ongewijzigd, terwijl kwetsbare oudere patiënten een afname van 39% vertoonden in morfineklaring via andere routes en voor M3G-eliminatie een toename van 43% in vergelijking met IC-patiënten. Over het algemeen had dit minimale invloed op concentratie-tijdprofielen bij bolusdoses, terwijl bij continue infusie dit resulteerde in een 20% verschil in steady-state concentratie. Dit lijkt in onze populatie klinisch van belang te zijn, gezien slechts 18% een adequate analgetische respons liet zien, terwijl er in 82% van de patiënten sprake was van oversedatie en in 50% van de patiënten van ernstige pijn. Een gestandaardiseerd postoperatief pijn protocol leidt dus tot een grote variatie in analgetische respons bij kwetsbare ouderen. Desondanks konden wij geen significant verschil aantonen tussen de correlatie van morfine of M3G concentraties en NRS scores. In toekomstige klinische onderzoeken moeten PKPD-simulaties met verschillende doseringsintervallen worden geëvalueerd om de blootstelling,

werkzaamheid en veiligheid van morfinedosering bij het starten van opioïd therapie bij kwetsbare oudere patiënten goed vast te kunnen stellen.

Samenvattend biedt dit proefschrift inzicht in nieuwe risicofactoren voor postoperatieve complicaties en functionele achteruitgang bij kwetsbare oudere patiënten na hartchirurgie. Om de bevindingen van het onderzoek dat in dit proefschrift wordt gepresenteerd in een breder perspectief te plaatsen, biedt **hoofdstuk 7** een reflectie op onze resultaten en aanbevelingen voor klinische zorg en vervolgonderzoek.



Appendix

List of publications

LIST OF PUBLICATIONS

Journal papers

Arends BC, Blussé van Oud-Alblas HJ, Vernooij LM, Verwijmeren L, Biesma DH, Knibbe CAJ, Noordzij PG, van Dongen EPA. The association of polypharmacy with functional decline in elderly patients undergoing cardiac surgery. Br J Clin Pharmacol. 2022.

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Arends BC, van Oud-Alblas HJB, van Dongen EP, Biesma DH, Vernooij LM, Noordzij PG. Continuous monitoring of vital signs and clinical deterioration in frail elderly cardiac surgery patients: AGE AWARE study: A prospective cohort study. Eur J Anaesthesiol. 2024.

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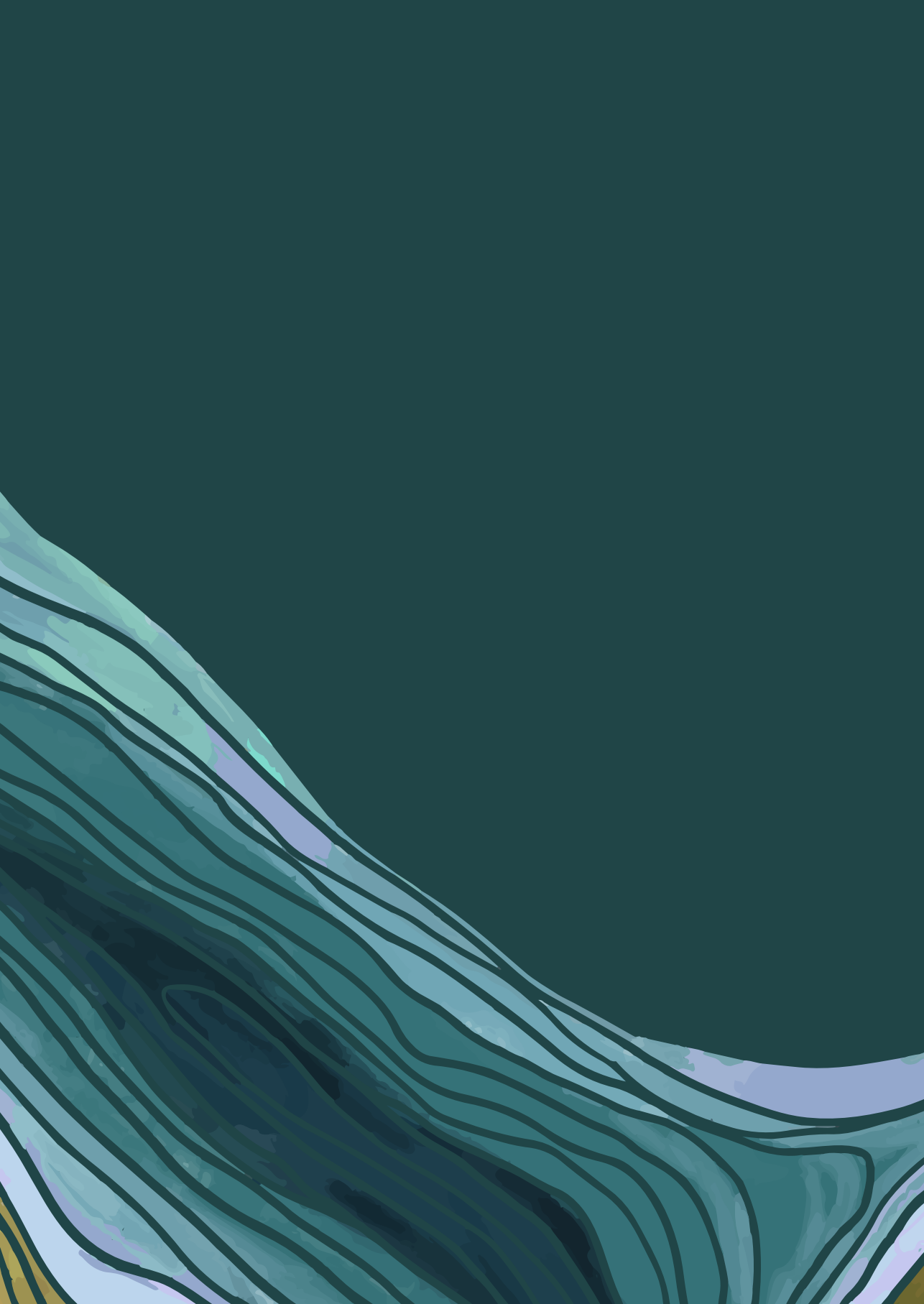

Appendix

List of abbreviations

LIST OF ABBREVIATIONS

AGE	anesthesia geriatric evaluation
AIC	akaike information criterion
aRR	adjusted relative risk
AUC	area under the curve
AUT	area under the threshold
AVPU	alert, verbal, pain, unresponsive
CFS	clinical frailty scale
CI	confidence interval
$CL_{e,M3G}$	elimination clearance of M3G
$CL_{m,M3G}$	morphine clearance through formation of the M3G metabolite
$CL_{non\text{-}M3G}$	morphine clearance through other routes
CNS	central nervous system
CWRES	conditional weighted residuals
EWS	early warning score
HER	electronic health record
EuroSCORE II	european system for cardiac operative risk evaluation II
EUSOS	european surgical outcomes study
GRIP	handgrip strength test
HR	heart rate
HRM	high risk medication
HRQL	health related quality of life
ICU	intensive care unit
IDI	integration discrimination improvement
IQR	interquartile range
LLOQ	lower limit of quantification
LRT	likelihood ratio test
M3G	morphine-3-glucuronide
MEWS	modified early warning score
MMSE	minimal mental state examination

MNA	mini nutritional assessment
NDPE	normalized prediction distribution error
NONMEM	nonlinear mixed effect modelling software
NRI	net reclassification improvement
NRS	numeric rating scale
NSAIDs	non-steroid anti-inflammatory drugs
OFV	objective function value
Oxycontin	oxycodone hydrochloride controlled-release
Oxynorm	oxycodone hydrochloride immediate-release
PD	pharmacodynamics
PK	pharmacokinetics
PPIs	proton pomp inhibitors
REDCap	research electronic data capture
REML	restricted maximum likelihood estimation
ROC	receiver operation characteristic
RR	respiratory rate
RRs	risk ratios
SD	standard deviation
SF-36	short-form 36 questionnaire
SpO_2	oxygen saturation
SSRIs	selective serotonin reuptake inhibitors
START	screening tool to alert to right treatment
STOPP	screening tool of older persons prescriptions
TCAs	tricyclic antidepressants
TGUG	timed get up & go test
TWA	time weighted average
WHODAS 2.0	world health organization disability assessment schedule 2.0
5-ML or 5-MWT	five-meter gait speed test
95% CI	95% confidence interval

Appendix

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LIST OF CONTRIBUTING AUTHORS

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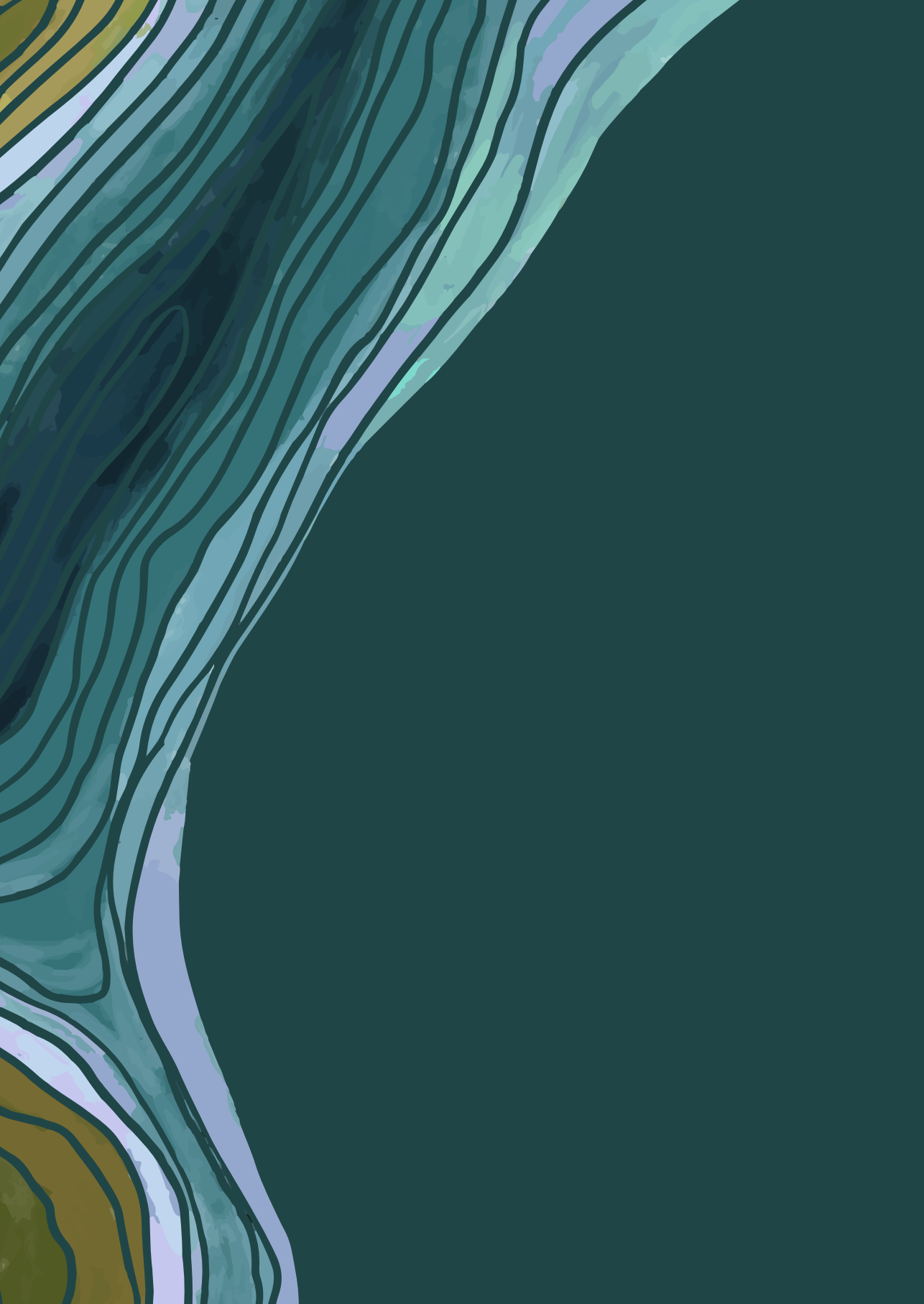

Appendix

Dankwoord

DANKWOORD

“Samen met anderen gaat alles beter, dacht de mier. Samen met anderen is alles lichter.”
– Toon Tellegen, Het vertrek van de mier

Het schrijven van dit proefschrift markeert het einde van een intensieve reis van ruim vijf jaar. Tijdens dit traject leerde ik mijzelf beter kennen, ging ik uitdagingen aan, en groeide ik zowel persoonlijk als professioneel. Dit boek was nooit tot stand gekomen zonder de steun, inspiratie en hulp van velen. Op deze plek wil ik enkele mensen in het bijzonder bedanken.

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Appendix

About the author

ABOUT THE AUTHOR

Britta Charèl Arends was born on January 25th 1993 in Zeist, the Netherlands. She graduated in 2011 from the Katholieke Scholengemeenschap de Breul in Zeist and thereafter started medical school at the Utrecht University. In her final year of medical school she followed a dedicated transitional year in vital functions including Anesthesiology, Cardiology, Intensive Care, Pulmonology and Emergency Medicine. Also, she expended her horizons through an internship ophthalmology in Vietnam and an extracurricular internship in tropical medicine in Malawi. During her elective research program her interest in research developed under the supervision of Dr. H.J. Blussé van Oud-Alblas at the St. Antonius Hospital in Nieuwegein.

After obtaining her Master's degree in 2018, she started to work as a resident not in training at the Intensive Care at the Gelre Hospital in Apeldoorn. In May 2019, Britta started her PhD research on the novel risk factors for poor functional outcome in frail cardiac surgery patients under the supervision of Prof. D.H. Biesma, Dr. H.J. Blussé van Oud-Alblas and Dr. P.G. Noordzij at the St. Antonius Hospital in Nieuwegein. During her PhD years, she set up multiple retrospective and prospective research projects, of which this thesis is the final product. In the course of the last year of her PhD research, her interest broadened from curing to prevention. After careful consideration, she switched career from Anesthesiology to Integrative Medicine. In September 2023 she joined the Academy of Integrative Medicine.

Currently, she runs her own practice as a physician specializing in lifestyle and integrative medicine. Combining a holistic approach with her passion for yoga, she helps individuals regain strength through personalized care, focusing on nutrition, lifestyle, and, when needed, conventional medicine.

After 2 years of renovations on their home, Britta and Daan now live happily together with their cat Knoffie and dog Maya in Utrecht, the Netherlands.

“The thing always happens that you really believe in,
and the belief in a thing makes it happen”

Frank Lloyd Wright