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Novel risk factors for poor outcome in frail cardiac surgery patients

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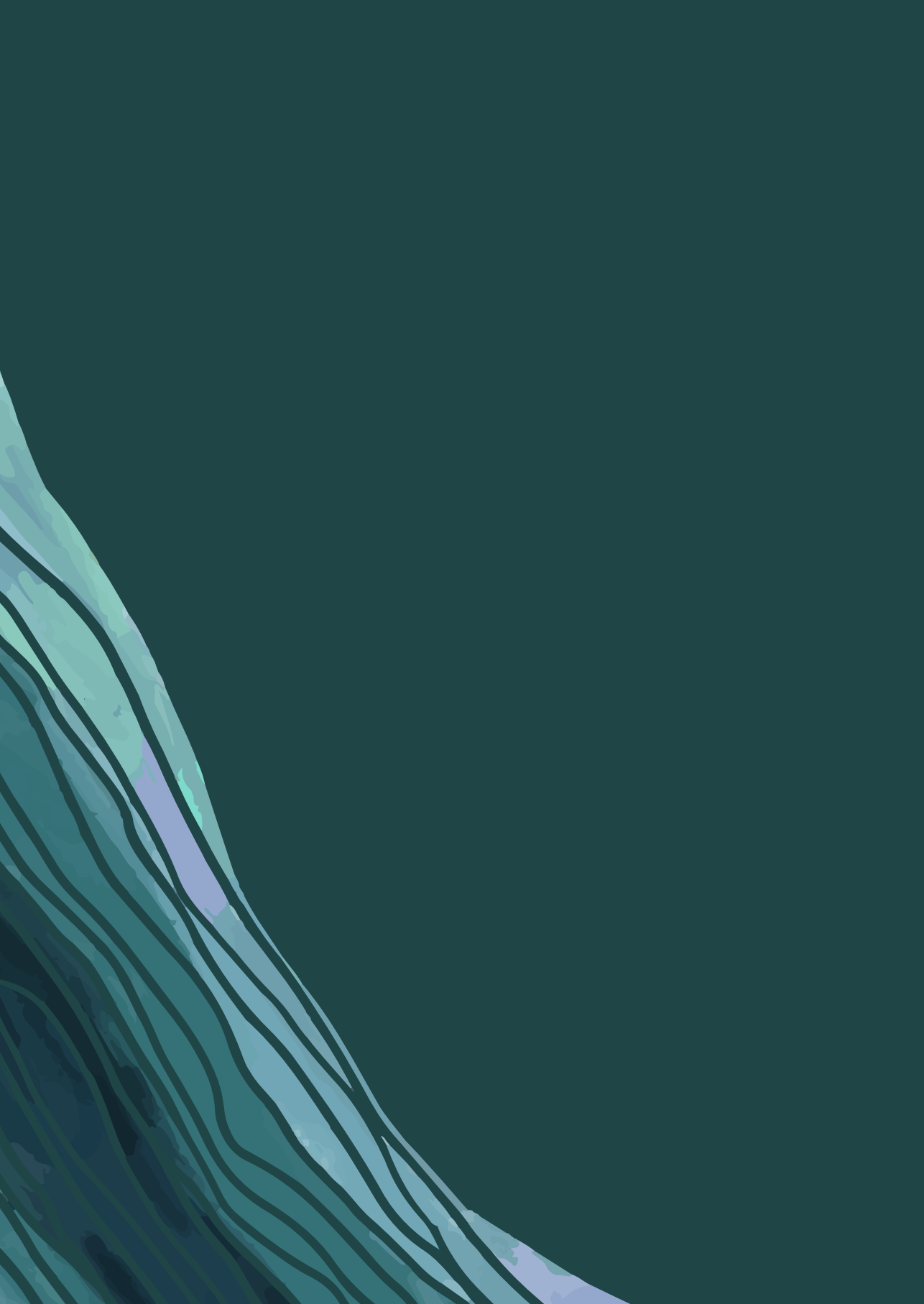

Appendix

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.