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Novel risk factors for poor outcome in frail cardiac surgery patients

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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 pump inhibitors 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, SpO₂ 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 SpO₂ levels in patients with underlying hypoxemia. In our study population, 77% of the frail elderly patients required a suppletion of >5L O₂. 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 T_{max} 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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