# Novel risk factors for poor outcome in frail cardiac surgery patients

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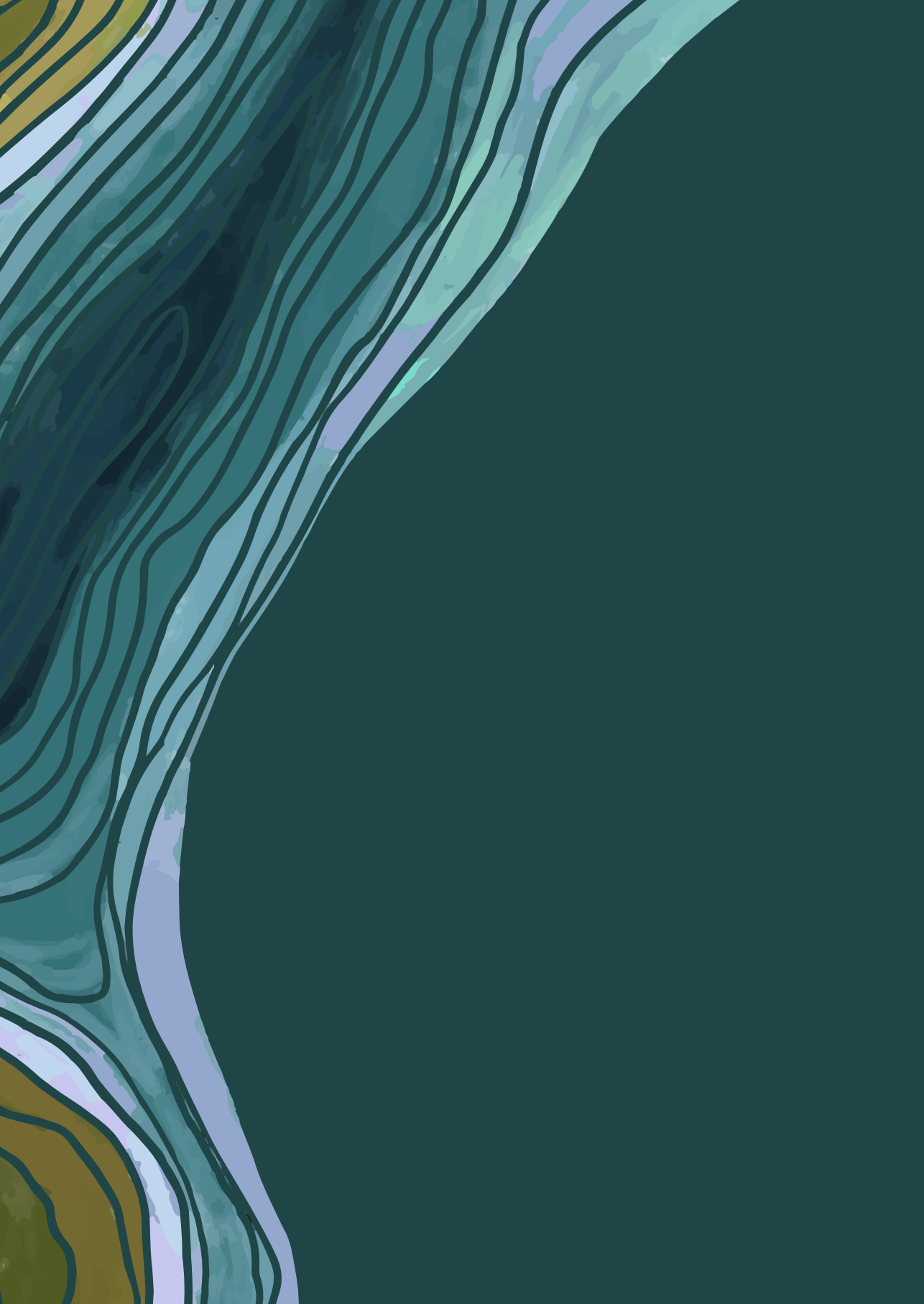

# Chapter 5

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

*a prospective observational study.*

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*Submitted*

# 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

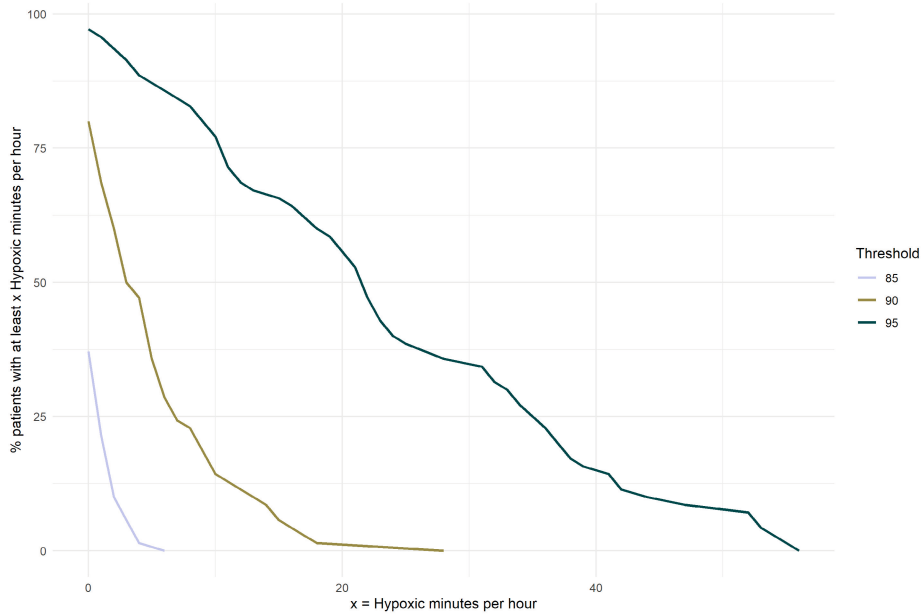
| Patient characteristics | HRM (n = 51) | No HRM (n=19) | P-value |
|---|---|---|---|
| Sex, male/female sex | 14/37 (28%/72%) | 7/12 (37%/63%) | 0.64 |
| Age, yrs | 75 (73.5 – 77.0) | 76 (74.5 – 79.0) | 0.18 |
| EuroSCORE II | 1.65 (1.33 – 2.77) | 2.01 (1.83 – 3.95) | 0.04 |
| Clinical Frailty Scale | | | 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

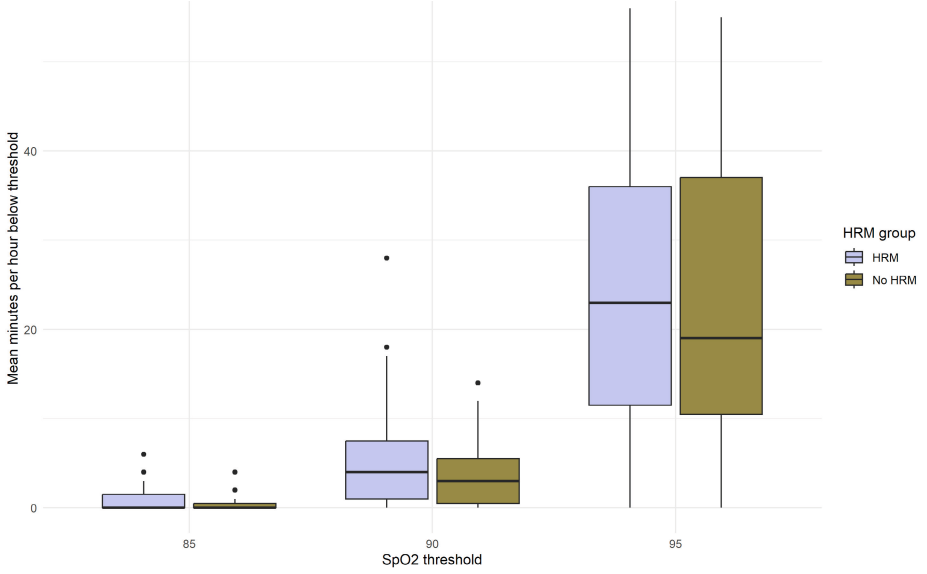
hours after admission at the general ward. During the period of maximum treatment effect, HRM was not associated with an increased risk of recurrent hypoxemia (adjusted RR 1.21, 95% CI 0.74 – 2.01, P=0.47). However, patients with HRM had more hypoxemic episodes (336 versus 126 episodes for patients without 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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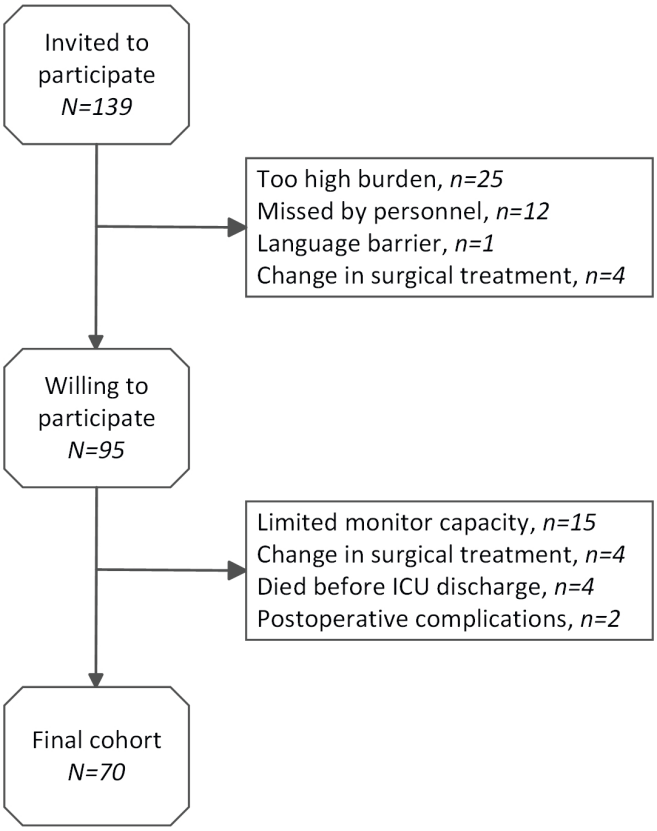
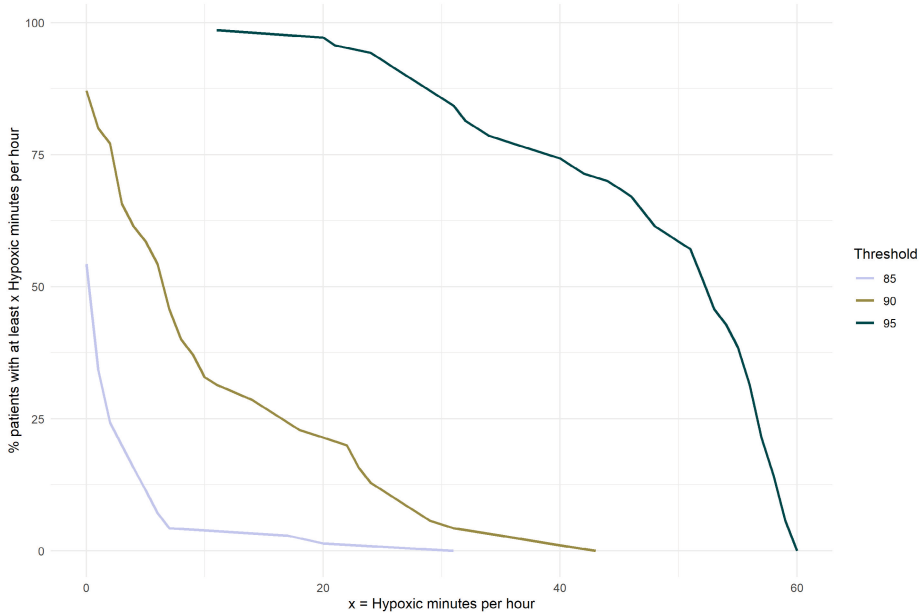
# SUPPLEMENTARY MATERIAL

**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.*