Novel risk factors for poor outcome in frail cardiac surgery patients

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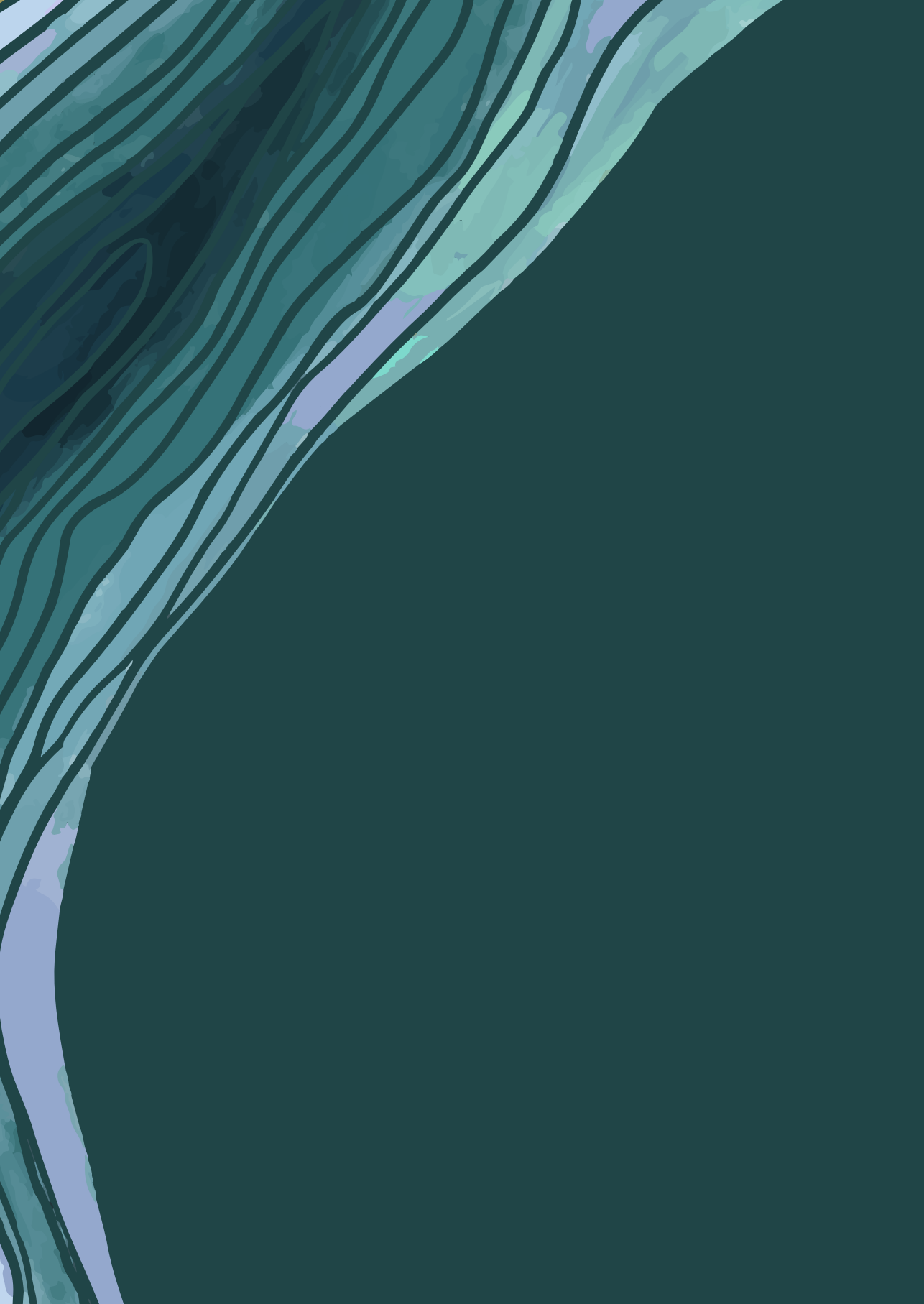

Chapter 2

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

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Br J Clin Pharmacol. 2022 May;88(5):2372-2379

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

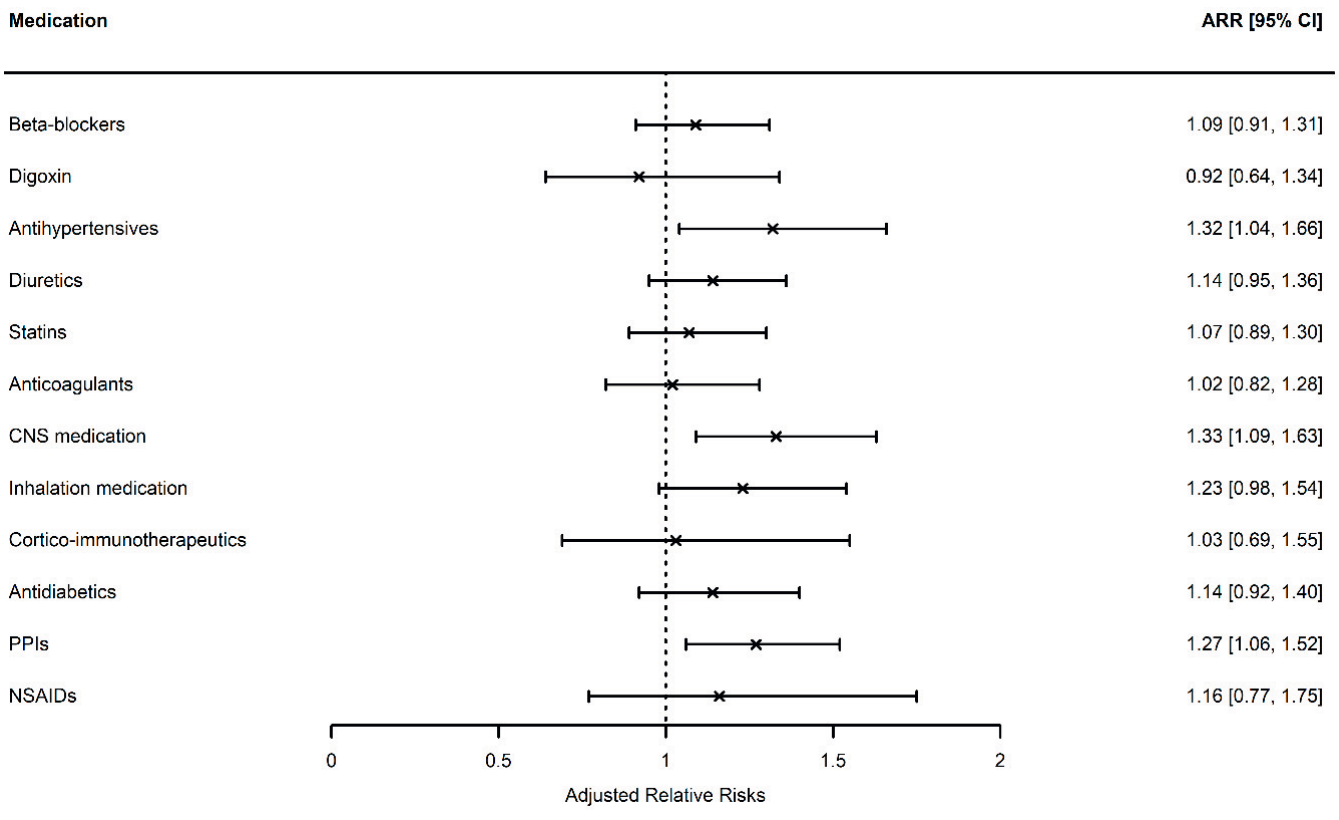
A total of 284 patients (55%) had functional decline one year after surgery, of which 63% was caused by disability and 37% due to worse HRQL. Patients with excessive polypharmacy had the highest incidence of functional decline (73%), compared to patients with polypharmacy (58%) and patients without polypharmacy (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.

ACKNOWLEDGEMENTS

None

REFERENCES

1. Khezrian M, McNeil CJ, Murray AD, Myint PK. An overview of prevalence, determinants and health outcomes of polypharmacy. Ther Adv drug Saf. 2020.
2. Midão L, Giardini A, Menditto E, Kardas P, Costa E. Polypharmacy prevalence among older adults based on the survey of health, ageing and retirement in Europe. Arch Gerontol Geriatr. 2018.
3. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: A systematic review. J Am Geriatr Soc. 2014.
4. McIsaac DI, Wong CA, Bryson GL, Van Walraven C. Association of Polypharmacy with Survival, Complications, and Healthcare Resource Use after Elective Noncardiac Surgery: A Population-based Cohort Study. Anesthesiology. 2018.
5. Partridge JSL, Harari D, Dhesi JK. Frailty in the older surgical patient: A review. Age Ageing. 2012.
6. Afilalo J, Mottillo S, Eisenberg MJ, et al. Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. Circ Cardiovasc Qual Outcomes. 2012.
7. Verwijmeren L, Peelen LM, van Klei WA, Daeter EJ, van Dongen EPA, Noordzij PG. Anaesthesia geriatric evaluation to guide patient selection for preoperative multidisciplinary team care in cardiac surgery. Br J Anaesth. 2020.
8. Whiteman AR, Dhesi JK, Walker D. The high-risk surgical patient: A role for a multidisciplinary team approach? Br J Anaesth. 2016.
9. Rubenstein LZ, Harker JO, Salvà A, Guigoz Y, Vellas B. Screening for undernutrition in geriatric practice: Developing the Short-Form Mini-Nutritional Assessment (MNA-SF). Journals Gerontol - Ser A Biol Sci Med Sci. 2001.
10. Huisman MG, Van Leeuwen BL, Ugolini G, et al. "Timed Up & Go": A screening tool for predicting 30-day morbidity in onco-geriatric surgical patients? A multicenter cohort study. PLoS One. 2014.
11. Sultan P, Hamilton MA, Ackland GL. Preoperative muscle weakness as defined by handgrip strength and postoperative outcomes: A systematic review. BMC Anesthesiol. 2012.
12. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975.
13. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (Sf-36): I. conceptual framework and item selection. Med Care. 1992.
14. Aaronson NK, Muller M, Cohen PDA, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998.
15. O'mahony D, O'sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. Age Ageing. 2015.
16. Blokzijl F, Houterman S, Van Straten BHM, et al. Quality of life after coronary bypass: A multicentre study of routinely collected health data in the Netherlands. Eur J Cardio-thoracic Surg. 2019.
17. Üstün TB, Chatterji S, Kostanjsek N, et al. Developing the world health organization disability assessment schedule 2.0. Bull World Health Organ. 2010.
18. Shulman MA, Myles PS, Chan MTV, McIlroy DR, Wallace S, Ponsford J. Measurement of disability-free survival after surgery. Anesthesiology. 2015.
19. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RHH. Overestimation of risk ratios by odds ratios in trials and cohort studies: Alternatives to logistic regression. CMAJ. 2012.

20. Bjørnnes AK, Parry M, Falk R, Watt-Watson J, Lie I, Leegaard M. Impact of marital status and comorbid disorders on health-related quality of life after cardiac surgery. Qual Life Res. 2017.

21. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for some traditional and novel measures. *Epidemiology*. 2010.

22. Cook NR. Quantifying the added value of new biomarkers: how and how not. *Diagnostic Progn Res*. 2018.

23. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. J Stat Softw. 2015.

24. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: A gentle introduction to imputation of missing values. J Clin Epidemiol. 2006.

25. Cooper JA, Cadogan CA, Patterson SM, et al. Interventions to improve the appropriate use of polypharmacy in older people: A Cochrane systematic review. BMJ Open. 2015.

26. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. Lancet. 2007.

27. McLachlan AJ, Bath S, Naganathan V, et al. Clinical pharmacology of analgesic medicines in older people: Impact of frailty and cognitive impairment. Br J Clin Pharmacol. 2011.

28. Fick DM, Semla TP, Steinman M, et al. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019.

29. Nehra AK, Alexander JA, Loftus CG, Nehra V. Proton Pump Inhibitors: Review of Emerging Concerns. Mayo Clin Proc. 2018.

30. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: A systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc. 1999.

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.