PREDICTING AND PREVENTING POSTOPERATIVE DECLINE IN OLDER CARDIAC SURGERY PATIENTS

ROELOF ETTEMA

Predicting and preventing postoperative decline in older cardiac surgery patients

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(met een samenvatting in het Nederlands)

Proefschrift

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Voor onze oudere medemens

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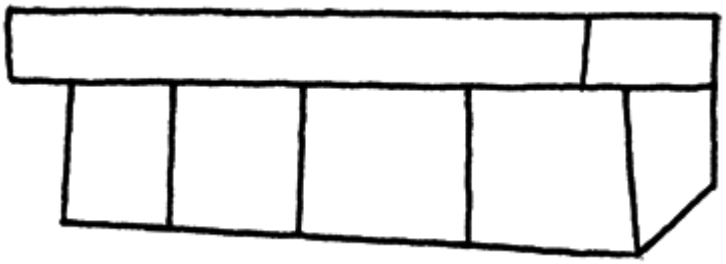
Introduction

Predicting and preventing postoperative decline in older cardiac surgery patients



INTRODUCTION

As a result of improved surgical and anaesthetic techniques cardiac surgery can be safely provided to older patients with chronic conditions, including frail patients.[1,2] Nowadays approximately 60% of the patients undergoing cardiac surgery is 65 years and older, and this proportion is still increasing.[1-4] The majority of those patients, fortunately, has an uncomplicated post-surgical course.[1,2,5,6]

An increasing proportion of the cardiac surgical patient population, however, experience one or more postoperative complications.[7-10] Delirium, depression, pressure ulcers and infection are frequently occurring.[11-29] These complications have an hampering effect on the recovery of patients and are associated with functional and cognitive decline, and with a decrease in quality of life after discharge.[7,8,30-32]

Frail older cardiac surgery patients, who are vulnerable to physical or emotional harm, are more likely to experience postoperative complications (see figure 1).[7,33-36] This increased risk is not necessarily related to the reason for surgery; rather, many of these complications are the result of hospitalization itself. Factors related to hospitalization – such as bed rest – have much more influence on development of complications in older patients than the surgery procedure itself, and these factors can cause a decline in their health condition.[7-9,30,31,37] Very often this decline already starts before the hospital admission. These patients often enter the hospital with a below average health condition and in order to reduce their risk on postoperative complications, they should be selected for preadmission preparation.[34,38,39] However, it is unclear which preadmission patient characteristics are associated with the occurrence of postoperative delirium, depression, pressure ulcer or infection.

It is widely accepted that vulnerable patients should be identified and optimally prepared before a cardiac surgery procedure.[35,36,40-42]As more than 95% of the cardiac surgery procedures is conducted electively, most patients have a waiting time before admission. Hence, there is indeed a window of opportunity to optimize the patient's condition before hospital admission (See figure 2).

In order to prevent adverse events in the postoperative period, in the past several attempts have been made to better prepare cardiac surgery patients in the preadmission period.[33,42-44] These interventions were limited to prevent either postoperative pulmonary complications or depression and were not designed to prevent all four postoperative delirium, depression, pressure ulcer and infection. Moreover, a thorough preadmission preparation is generally not part of the standard cardiac surgery (preoperative) pathway.

This pathway is commonly limited to the period of hospitalization and does not comprise actions to improve the patient's health condition before admission.[45]

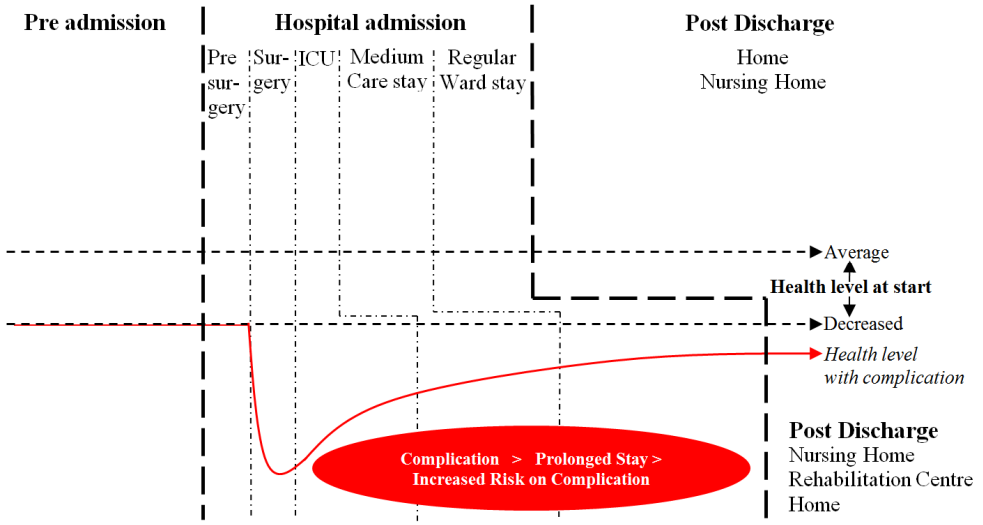


Figure 1 *Theoretical clinical course of a patient with a decreased health level undergoing cardiac surgery who develops a postoperative complication and experience a prolonged hospital stay. The upper dashed horizontal line represents the average health level of a patient before admission and the lower horizontal line represents the health level of a patient with decreased health level before admission*

Patient care before hospital admission

Also, in particular in frail older people, postoperative complications are often influenced by multiple common and comorbid health problems, which are multifactorial in etiology and in which more than one risk factor is involved.[1,3,10,] An effective intervention should therefore ideally address this multifactorial origin.[39,41,46] When preparing older patients for cardiac surgery in the preadmission period with the aim to reduce the risk of multiple complications, a multi component intervention is therefore desirable.[33,43,47,48] It is however unknown which elements should be part of such a multicomponent intervention to reduce the risk of postoperative complications in older cardiac surgery patients and how much reduction in the rate of postoperative complications can be achieved with optimal preoperative preparation.

Improving the physical condition of a patient in order to optimize the outcome of hospital stay is typically one of the fundamental roles of nursing care.[49,50] Therefore in our

opinion nurses should play an important role in preadmission preparation of patients undergoing cardiac surgery.

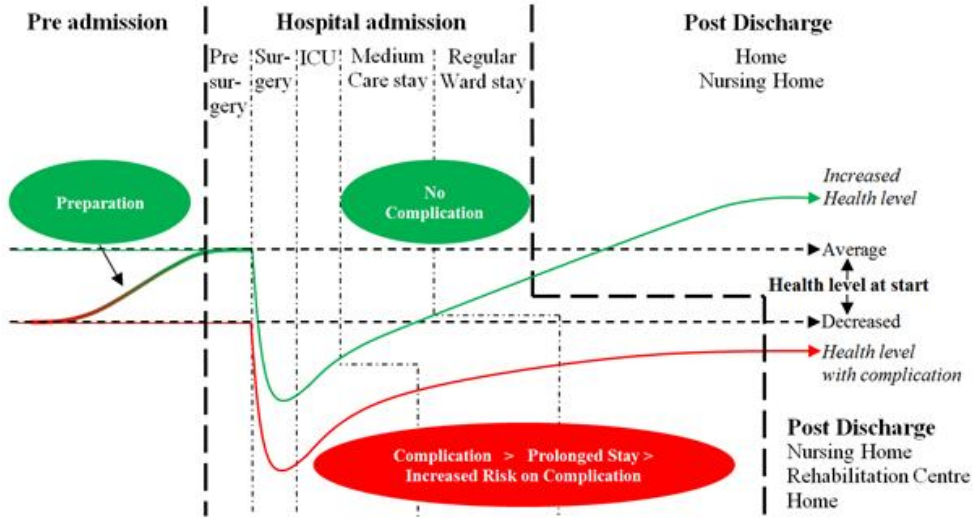


Figure 2 *Proposed effect of patient care before hospital admission of a cardiac surgery patient at risk for postoperative complications. The upper dashed horizontal line represents the average health level of a patient before admission and the lower horizontal line represents the health level of a patient with decreased health level before admission*

Aim and outline of the thesis

In this thesis we first focused on identification of patients with an increased risk on postoperative complications, and subsequently we focused on developing a nursing intervention which can be applied in the period between the indication for surgery and the actual admission to the hospital.

The aim of this thesis is twofold:

1. To identify in the preadmission period older cardiac surgery patients at risk for postoperative delirium, depression, pressure ulcers or infection.
2. To provide nurses with an intervention for preparing these older patients before their hospital admission to prevent postoperative delirium, depression, pressure ulcers or infection.

The first part of the thesis addresses the question how to identify patients at increased risk of the four postoperative complications. In *chapter 1*, we systematically reviewed the

literature for models predicting a prolonged intensive care unit stay in patients undergoing cardiac surgery, as these models are generally used as a proxy for surgical and intensive care unit complications. Subsequently, we applied the identified models to a large dataset with patients of all ages to identify the models with the best performance.

In order to study the performance of those models in older patients, we quantified the changes in performance of the three best performing models from chapter 1 with increasing age of patients in *chapter 2*.

In *chapter 3* we focused on identifying older patients with an increased risk on postoperative delirium, depression, pressure ulcers or infection at two to four weeks before admission. This chapter describes a study in which we developed prediction models for those postoperative complications, which can be applied in older patients scheduled to undergo cardiac surgery.

The second part of the thesis focuses on development of an intervention programme for older patients undergoing cardiac surgery to increase their physical and psychosocial condition before surgery, in order to reduce their risk of postoperative complications. In *chapter 4* we systematically reviewed the literature on preadmission interventions designed to prevent postoperative complications. The results of this systematic review formed a base for developing a preventive intervention.

Chapter 5 presents the development of the evidence based multi component nursing intervention (PREDOCS programme). It gives a detailed description of the process used to design and develop this multi component intervention and the multi component nursing intervention itself.

Finally, chapter 6 describes a study in which we tested the PREDOCS programme on its feasibility for application by nurses in the preadmission period in a, with respect to frailty, heterogeneous population of 70 older cardiac surgery patients in three hospitals in the Netherlands.

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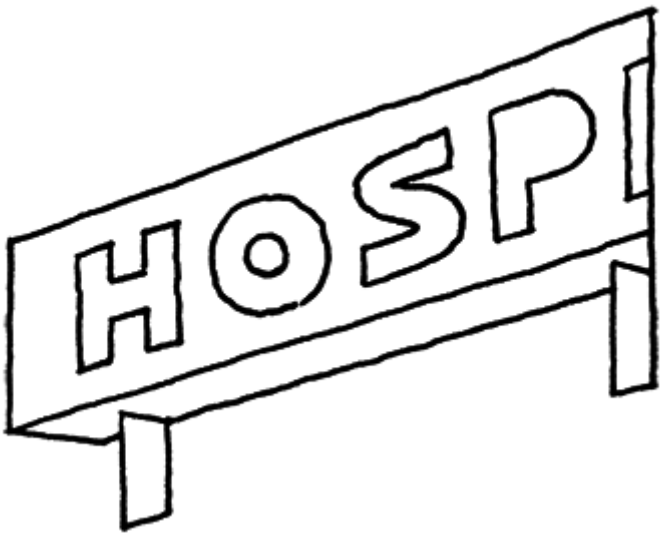
Part 1

Selecting older patients at risk for postoperative complications

Chapter 1

Prediction models for prolonged intensive care unit stay after cardiac surgery: systematic review and validation study



Ettema RG, Peelen LM, Schuurmans MJ, Nierich AP, Kalkman CJ, Moons KG.
Circulation 2010;122:682-9.

ABSTRACT

Background: Several models have been developed to predict prolonged stay in the Intensive Care Unit (ICU) after cardiac surgery. However, no extensive quantitative validation of these models has yet been conducted. This study sought to identify and validate existing prediction models for prolonged ICU length of stay after cardiac surgery.

Methods and Results: After a systematic review of the literature, the identified models were applied on a large registry database comprising 11,395 cardiac surgical interventions. The probabilities of prolonged ICU length of stay based on the models were compared to the actual outcome to assess the discrimination and calibration performance of the models.

Literature review identified twenty models, of which fourteen could be included. Of the six models for the general cardiac surgery population, the Parsonnet model showed the best discrimination (area under the receiver operating characteristic curve: 0.75 [95% CI = 0.73-0.76]), followed by the EuroSCORE (0.71 [0.70-0.72]) and a model by Huijskes and colleagues (0.71 [0.70-0.73]). Most of the models showed good calibration.

Conclusion: In this validation of prediction models for prolonged ICU length of stay, two widely implemented models (Parsonnet, EuroSCORE), although originally designed for prediction of mortality, were superior in identifying patients with prolonged ICU length of stay.

KEYWORDS

Cardiovascular Diseases, Risk Factors, Complications, Surgery, Epidemiology

INTRODUCTION

In the past decades, mortality during, or shortly after cardiac surgery has decreased[1]. However, morbidity has increased[2], mainly because cardiac surgery is increasingly utilised in older and more vulnerable patients. This often results in more complications after surgery and potential reduction in quality of life[3-5]. One method of assessing complications occurring directly after cardiac surgery is a prolonged stay in the Intensive Care Unit (ICU)[6-9]. Prolonged ICU stay also leads to incremental use of resources. In practice prediction models are being used for efficient use of ICU resources. Patients with a low risk on complications are being schedules for surgery before patients with a high risk[5-13]. Various prediction models have been developed to preoperatively identify patients with an increased risk for postoperative complications and prolonged ICU stay[12-28]. Interestingly, all of these prediction models were derived from samples including different patients, as reflected by the different distributions of patient and outcome characteristics. Hence, which model should be preferred in which situation is still unclear. Recently, in a qualitative review, Messaoudi and colleagues[14] reviewed thirteen of these prediction models by comparing their published prognostic values for predicting ICU stay. They found that the thirteen different prediction models indeed used different definitions of prolonged ICU stay and different definitions of predictors.

Even though it is widely accepted that no prediction model should be applied in practice before being formally validated on its predictive accuracy in new patients[29-31] no study has previously performed a formal, quantitative (external) validation of these prediction models in an independent patient population. Therefore, we first conducted a systematic review to identify all existing prediction models for prolonged ICU length of stay (PICULOS) after cardiac surgery. Subsequently, we validated the performance of the identified models in a large independent cohort of cardiac surgery patients.

METHODS

Systematic literature review

In February 2008, the MEDLINE and PreMEDLINE databases were searched for studies concerning prediction models for PICULOS after cardiac surgery that were published after 1980. The precise search query is presented in Appendix 1.

The retrieved articles were reviewed by two reviewers (RE and LP) and retained when they presented a formally developed prediction model. There is no consensus on the exact definition of PICULOS[14]. To relate to clinical practice[2,11,13,15-28], we further restricted our analysis to prediction models that used a threshold for PICULOS within the bounds of 24-72 hours.

Application of the models to an independent cohort

The validation of the retrieved models was then performed on a large cohort of cardiac surgery patients who underwent surgery between January 1st, 2000 and July 31st, 2008 at the Isala Clinics, Zwolle, the Netherlands (1,400 cardiac surgery procedures per year). The data had been prospectively collected as part of a continuous data registry for the national cardiac surgery patient registration. All patients provided informed consent to use the data for research. Patients' identifying information was removed before the analysis.

When the original articles did not provide sufficient information on the included predictors or regression coefficients (log odds ratios) in the model, the authors were asked to personally provide this information. If the information obtained was insufficient to apply the model to our data, the study was excluded from the analysis.

To validate the performance of the retrieved models, we used the original formulas and applied them to our patients using their observed predictor values. This yielded a predicted probability of PICULOS for each patient based on each model. To do this, we first matched the predictors in each prediction model to the variables in our data set. When a predictor was not available in our data set, we proceeded as follows. First, we sought to replace the variable with a proxy variable. Second, if a proxy was not available, we imputed the incidence or mean value reported in the literature for these predictors[32-34]. To prevent overimputation, this option was applied only when the weight of the predictor in the corresponding prediction model was relatively low compared to the other predictors in that model because it has a tempering effect on the predictive ability of the model. As a consequence, we only used this method for the predictors 'Family history' in the Parsonnet model[35,36] and 'preoperative Hb level' in the model of Huijskes et al.[17,37]. If neither of these methods could be applied, the model was excluded from the analysis[13,25].

Data analysis

To analyse the performance of each prediction model, each patient's predicted probability of PICULOS in each model was compared to the observed outcome, (i.e., whether the patient had actually experienced PICULOS [yes/no]). To allow for a fair comparison of the models, a threshold for observed PICULOS had to be chosen. Based on the literature[15,17,21,22,25,26,28] and current clinical practice, we defined observed PICULOS as an ICU length of stay of more than 48 hours.

In comparing the performance of the models, we focused on discrimination and calibration. The *discrimination* performance of a model indicates the extent to which the model distinguishes between patients with and without prolonged ICU stay. The discrimination performance of the models was expressed by constructing receiver operating characteristic curves for each of the models and calculating the area under the curves (AUCs) with a 95% confidence interval[38]. Theoretically, the AUC ranges from 0.5 (no predictive ability at all) to 1 (perfect predictive ability). In practice however, the AUC

can be well below the theoretical maximum of 1 even if the prediction model is perfectly calibrated, especially in complex diseases[39].

The *calibration* performance of a model describes the extent to which the predicted probability of prolonged ICU stay reflects the true probability of prolonged ICU stay. The calibration of the models was judged by constructing calibration plots[40], relating the predicted and observed probabilities. The calibration performance of a prediction model in an independent dataset (external validation set) is commonly influenced by the incidence of the outcome in the validation set.

To allow for a fair comparison of the models, we adjusted the intercept of each model before applying it to the data, such that the mean predicted probability was equal to the observed outcome frequency[34,41]. Calibration plots were constructed subsequently. For each model, the *U*-statistic (which compares the actual slope and intercept of the calibration plot to the ideal values of 1 and 0 respectively) was calculated and tested against a χ^2 distribution with two degrees of freedom[33].

To further measure the accuracy of the models we calculated the Yates slope (difference between the mean predicted probabilities for the patients with and without actual prolonged ICU stay), and the Brier scores (quadratic difference between predicted probability and actual outcome [0 or 1] for each patient) for each of the models[42]. All these measures give insight into the distance the model creates between the patients with and without prolonged ICU stay.

Missing values occurred for the variables “gender” (0.05%), “myocardial infarction” (0.14%), “serum creatinine” (2.86%), “smoking“ (0.13%), “height” and “weight” (both 45% of cases), “New York Heart Associantion classes” (0.92%) and the outcome variable “ICULOS” (1.71%). Missing values were substituted by means of single regression and weighted mean imputation, both of which are widely known method for the substitution of missing values to reduce bias and increase statistical power[32]. Two-sided statistical tests were conducted with a significance level of 0.05. The statistical package R (version 2.10.1 (2009-12-14), The R Foundation for Statistical Computing, Vienna Austria) was used for statistical analysis.

RESULTS

Systematic literature review

Figure 1 shows the flow chart of the systematic literature review. From the 56 articles that matched the initial search query, 25 articles described 20 different prediction models[2,8,11-13,15-28,35,43,44]. Two models were excluded because they used a threshold of >72 hours to define prolonged ICU stay[8,12].

Additional information concerning intercepts, coefficients and definitions of predictors in the models was requested from the authors for seven models[11,15,16,24,25,27,35]. Two authors responded with the requested information[11,16], two authors responded but were not able to provide the requested information[15,27] and four authors did not respond.

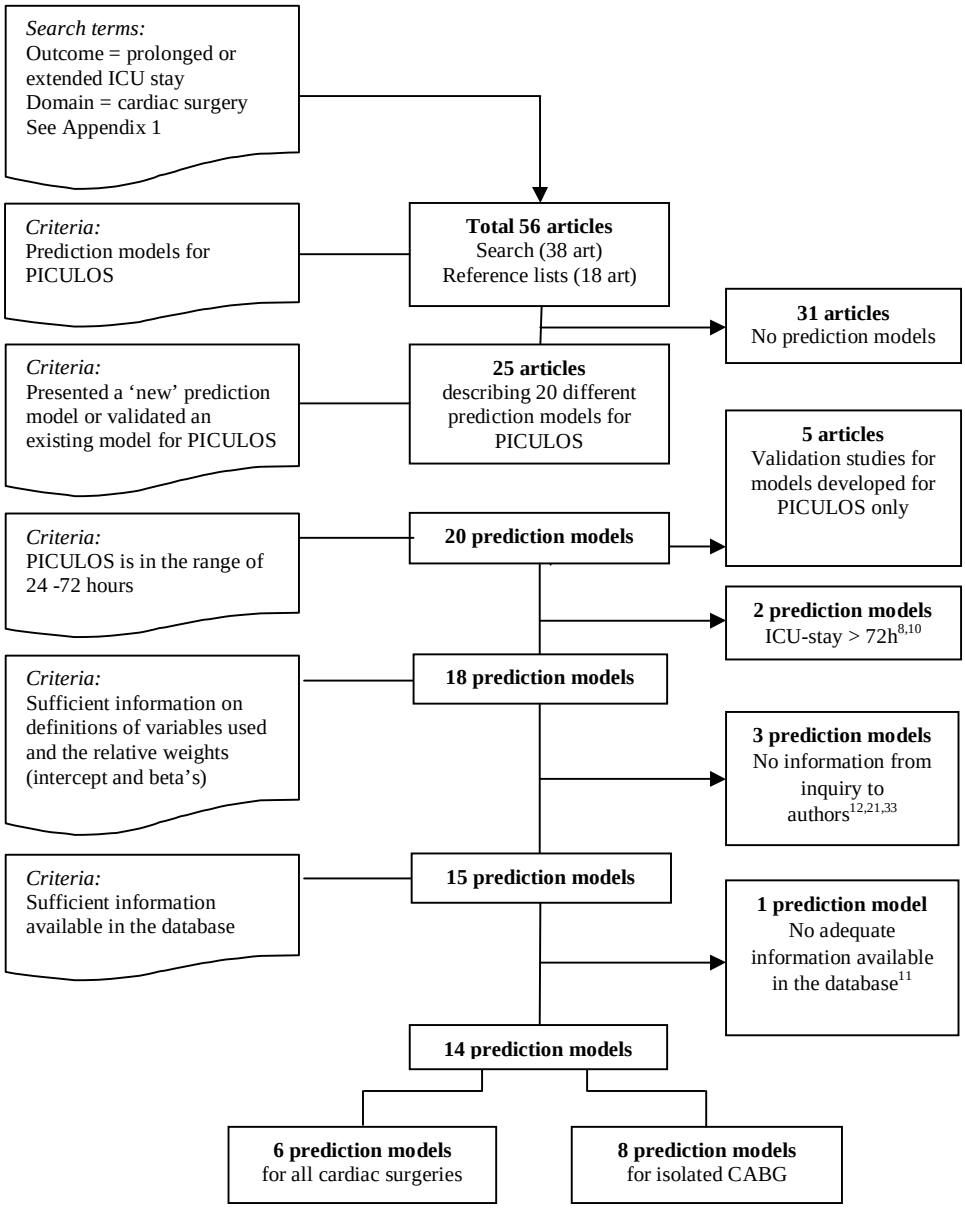
Table 1 describes the general characteristics of the fourteen selected prediction models. Appendix 2 provides a more extensive overview of the characteristics of the prediction models according to the framework established by Laupacis and colleagues[45].

Three models were excluded because necessary information on the definitions of the variables used was missing[10,15,25] and one model was excluded because no adequate information was available in the database[13] . Finally, fourteen prediction models could be included into our validation study.Six of these fourteen models were developed for patients undergoing cardiac surgery in general[17,21,26,27,35,43,44], whereas the eight other models focused on patients undergoing isolated Coronary Artery Bypass Grafting (CABG) surgery[2,16,18,,20,23,24,27]. Two of the fourteen prediction models, the Parsonnet model[35] and the EuroSCORE[43,44], were originally designed for the prediction of mortality after cardiac surgery, but have been used and validated for prolonged ICU stay[7, 8,11,21,28]. Therefore, these models were also included in our study.

Predictive performance

Table 2 describes the baseline characteristics of the patients in our cohort. We tested the prediction models in our cohort on the type of patients for which they were developed; prediction models developed for cardiac surgery in general were evaluated on all patients (n = 11,395); prediction models developed for isolated CABG patients were evaluated on patients who underwent isolated CABG (n = 6,463) only.

Figure 2 depicts the ROC curves for each of the models and Table 3 depicts the accompanying statistics. Among models including all cardiac surgeries, the Parsonnet model[8,11,35] showed the best discrimination (AUC 0.75 [95% confidence interval 0.73-0.76]), followed by the EuroSCORE[7,21,28,43,44] (0.71 (0.70-0.72)) and a model by Huijskes and colleagues[17] (0.71 [0.70-0.73]). Among the models specifically developed for patients undergoing isolated CABG, the models by Wong[23], Ivanov[20] and Tuman[27] showed the best discrimination, with AUCs of 0.68 (0.65-0.70), 0.67 (0.65-0.70) and 0.66 (0.64-0.68) respectively.



ICU = Intensive Care Unit
PICULOS = Prolonged Intensive Care Unit Length Of Stay
CABG = Coronary Artery Bypass Grafting

Figure 1 *Flowchart of the systematic review of prediction models for prolonged ICU stay after cardiac surgery*

Table 1 General characteristics of the studied prediction models

	YEAR OF PUBL.	PERIOD OF DATA COLLECT.	REGION (NUMBER OF CENTRES)	NO. OF SUBJ. IN DERIV. SET	ORIGINAL OUTCOME	NO. OF PREDIC-TORS	AUC IN INITIAL PUBLICATION	P-VAL. HL G-O-F IN INIT. PUBL.
CARDIAC SURGERY								
Parsonnet [35]	1989	1982-1987	USA(1)	3,500	> 24hours*	17	0.7*	n.r.
Tuman [27]	1992	n.r.	USA(1)	3,156	‡	16	n.r.	n.r.
Tu [26]	1994	1990-1991	Canada(1)	713	>2days	10	0.69	0.24
EuroSCORE [43,44]	1999	1995	Europe(132)	13,302	>2days†	20	0.78† 0.76&0.79§†	0.4†
Pitkänen [21]	2000	1992-1996	Finland(1)	3,061	>2days	12	0.75&0.81§	0.4&0.48§
Huijskes [17]	2003	1997-2001	Netherlands(1)	4,843	>2days	14	0.79&0.78‖	0.63&0.36‖
ISOLATED CABG SURGERY								
Tuman [27]	1992	n.r.	USA(1)	3,156	‡	11	n.r.	n.r.
Christakis [24] #	1996	1990-1992	Canada(1)	889	>3days	4	n.r.	n.r.
Wong [23]	1999	1995	Canada(1)	885	>2days	9	0.89&0.85**	n.r.
Ivanov [20]	2000	1993-1997	Canada(2)	5,354	>2days	17	0.71	0.51
Janssen [18]	2004	2000-2001	Netherlands(1)	888	≥3days	6	n.r.	n.r.
Abrahamyan [16]	2006	2003	Armenia(1)	391	≥3days	4	0.71	0.6
Ghotkar [2]	2006	1997-2002	England(1)	5,168	>3days	14	0.72&0.74‖	0.3&0.79‖

HL = Hosmer-Lemeshow (p-value of the Hosmer-Lemeshow goodness-of-fit statistic)

n.r. = not reported

CABG = Coronary Artery Bypass Grafting

* Originally developed for mortality, validated for Prolonged ICU Length Of Stay (PICULOS) by Hsieh et al. 2007 [8]; Lawrence et al. 2000 [11]

† Originally developed for mortality, validated for PICULOS by Pina Pintor et al. 2003 [7]; Pitkänen et al. 2000 [21]; Nilsson et al. 2004 [28]

‡ Group of patients with a mean ICU stay of 2.5 (± 0.4 days) compared to group of patients with a mean ICU stay of 7.0 (± 9.6 days)

§ Figures based on a retrospective dataset and a prospective dataset, respectively

‖ Figures based on a derivation set and a validation set, respectively

Two models were provided: one model containing only preoperative predictors (Christakis I) and one model containing both preoperative and postoperative predictors (Christakis II)

** Figures based on a derivation set and bootstrap validation, respectively

Figures 3a and 3b show calibration plots of the two best and the two least performing models after adjustment of the intercept of each model for all cardiac surgery patients and isolated CABG patients, respectively. For most of the models, the calibration line in the plot closely followed the ideal calibration line**,** except for the models of Wong[23] and Abrahamyan[16]. The six models for the general cardiac surgery population had low P-values for the *U*-statistic (Table 3), indicating that the six models do not provide accurate probabilities. For the isolated CABG surgery patients only the Tuman[27] and Christakis-I[24] models had non-significant p-values.

DISCUSSION

We conducted a systematic review and validated the performance of fourteen retrieved prediction models to identify patients with prolonged ICU stay after cardiac surgery, using a large cohort of cardiac surgery patients. In this first quantitative comparison of all prediction models to identify patients who are likely to have a prolonged ICU stay, the Parsonnet model and the EuroSCORE show the best performance in terms of discrimination accuracy, and calibration. Although both models were originally developed to predict mortality, we have found that they are also superior in identifying patients with an increased risk of prolonged ICU stay. A major explanation lies in the fact that, in current practice, mortality has decreased but morbidity has increased[1,2]. Due to advances in perioperative care in cardiac surgery[46], most of the patients who were likely to die in the era when Parsonnet's model and the EuroSCORE were developed will now survive, but they still have a higher probability of developing complications. This is also supported by Parolari and colleagues[47], who noticed a significant overestimation of mortality with the EuroSCORE. Because both models over-estimate mortality in current practice, these models for mortality need to be corrected for improved level of care in the future.

In the systematic review, we found twenty prediction models for prolonged ICU stay, fourteen of which we could include in our analysis. In accordance with Messaoudi[14], we found considerable differences in the definitions of the predictors and outcomes. We chose to restrict our systematic review to prediction models that used a threshold for PICULOS within the bounds of 24-72 hours. Afterwards, in our validation study, we used the threshold of 48 hours, as this correlates best with clinical practice. To verify the extent to which this difference has influenced our findings, we have repeated the validation analysis using threshold values of 24 hours and 72 hours. This did not influence the ranking of the models based on their performance.

Table 2 Baseline characteristics of the patients in the database

	ALL CARDIAC SURGERY	*ISOLATED CABG*
Number of cases, n (% of total)	11,395 (100)	6,463 (56.7)
PICULOS*, n (incidence in %)	1,842 (16.1)	566 (8.8)
Female Gender, n (%)	3,397 (29.8)	1,564 (24.2)
Age, median (1^{st}Q, 3^{rd}Q)	67.8 (59.6,74.2)	66.8 (59.1,73.1)
ICU days, median (1^{st}Q, 3^{rd}Q)	0.92 (0.8,1.2)	0.91 (0.8,1.0)

Q indicates quartile.
*Defined as ICU length of stay >48 hours.

Substantial differences between the models were also found in the sizes of the databases used to develop the prediction models, and in the number of predictors in the models. Only ten of the fourteen models were initially validated, nine of which used an independent validation set[2,17,20,21,26,27,35,43,44], and one was validated by means of bootstrapping[23]. Prospective validation, however, was done for only four models[21,35,44]. In every case, the validation of the models was done in relatively small datasets (sizes ranging from 394[27] to 2,439[17]). Only Parsonnet's model[8,11], the EuroSCORE[7,21,28] and Tu's model[8] were validated by other authors in a different geographical region. Due to all these differences, the results of these original analyses are difficult to compare.

Our analysis is the first extensive quantitative validation of existing models for prolonged ICU stay after cardiac surgery in a large dataset including >11,000 patients. All models were validated on the same dataset, which allows for a proper comparison of the performance of the models.

To determine the calibration of the models, we made calibration plots and calculated the *U*-statistic and the Hosmer-Lemeshow statistic. At first sight, these approaches gave contradictory results. In most of the models, the Hosmer-Lemeshow - and *U*-statistics had a p-value <0.05, suggesting that the predictions based on the model deviated significantly from the observed data. In contrast, the calibration lines in the plots were very close to the 45^{O} line, suggesting near-perfect calibration. In order to gain insight in the cause of these large statistics we furthermore calculated the t-values for the slopes of the models. This revealed that the slopes of the models in this dataset deviate significantly from the ideal slope of 1. This would explain the large chi-square values even after recalibration by adjusting the intercepts only. Whereas calibration statistics are merely summary measures, calibration plots directly reveal the variation of the performance of the model over the entire range of probabilities[48].

Table 3 also shows the importance of recalibrating a model by adjusting the intercept[34,41] before calibration of the model is assessed. The mean predicted risks of the

original models do not even approach the observed outcome frequency, whereas after recalibration this problem is solved. This allows for a more fair comparison of the models and a better performance when the models are applied in daily practice.

Table 3 Predictive performance of the prediction models in the study cohort

	No.of predictors the model	*Yates Slope**	*Brier Score**	*Brier Scaled**	*AUC C-statistic**	*U-statistic P-val (χ)* Recalibr. models*	*Mean pred. risk ICU-LOS>48h* Recalibr. models*	*Mean pred. risk ICU LOS>48h* Not recal. models*
ALL CARDIAC N=11,395							*Incidence ICULOS>48h = 0.162*	
Parsonnet	17	0.157	0.122	0.065	0.75(0.73-0.76)	<0.000(100.61)	0.162	0.066
Tuman	16	0.079	0.128	0.064	0.67(0.66-0.69)	<0.000 (15.28)	0.162	NA †
Tu	10	0.099	0.129	0.064	0.69(0.68-0.71)	<0.000(154.88)	0.162	0.357
EuroSCORE	20	0.149	0.126	0.064	0.71(0.70-0.72)	<0.000(397.58)	0.162	0.877
Pitkänen	12	0.096	0.130	0.064	0.69(0.67-0.70)	<0.000(226.46)	0.162	0.206
Huijskes	14	0.155	0.127	0.064	0.71(0.70-0.73)	<0.000(305.96)	0.162	0.049
ISOLATED CABG N=6,463							*Incidence ICULOS>48h = 0.088*	
Tuman	11	0.046	0.076	0.115	0.66(0.64-0.68)	0.383 (1.92)	0.097	NA †
Christakis pre	4	0.014	0.080	0.115	0.59(0.56-0.61)	0.116 (4.31)	0.085	NA †
Christakis prepost	4	0.050	0.084	0.114	0.62(0.60-0.64)	<0.000(205.53)	0.095	NA †
Wong	9	0.135	0.076	0.114	0.68(0.65-0.70)	<0.000(474.92)	0.103	NA †
Ivanov	17	0.082	0.080	0.115	0.67(0.65-0.70)	<0.000 (29.72)	0.090	0.299
Jansen	6	0.048	0.079	0.115	0.63(0.60-0.65)	<0.000 (78.33)	0.098	0.167
Abrahamyan	4	0.031	0.087	0.114	0.57(0.54-0.59)	<0.000(433.61)	0.089	0.767
Ghotkar	14	0.051	0.081	0.115	0.64(0.60-0.66)	<0.000 (83.61)	0.086	0.143

LOS indicates length of stay; NA, not applicable.

*) All statistics are scaled from 0 to 1. Higher Yates' slope as well as lower Brier Scores and higher Brier Scaled and higher discrimination C-statistics and non-significant p-values of the calibration *U*-statistic, represent better performance.

†) The mean predicted risk for these (not calibrated) models could not be calculated because the original intercepts where not provided for these models.

To determine the discrimination performance of the models, we calculated the AUCs. The six models for the general cardiac surgery population yielded AUCs ranging from 0.68 to 0.74. In the models specifically developed for patients with isolated CABG surgery, substantially lower AUCs (0.56-0.67) were found. In general, values for the AUC below 0.70 indicate that use of the model in clinical practice should be done with caution[49], as the

theoretical maximum value of the AUC is 1.0. However, it is also known that in practice this maximum not only depends on the model, but also on characteristics of the data[39]. To allow for better interpretation of our findings and provide a 'benchmark value', we fitted two reference models on the data (one for all patients, one for patients undergoing isolated CABG only), which yielded AUCs of 0.80 and 0.73 respectively. These models are likely to be overfit but give a reference value for interpretation of the AUCs of the prediction models found in the literature.

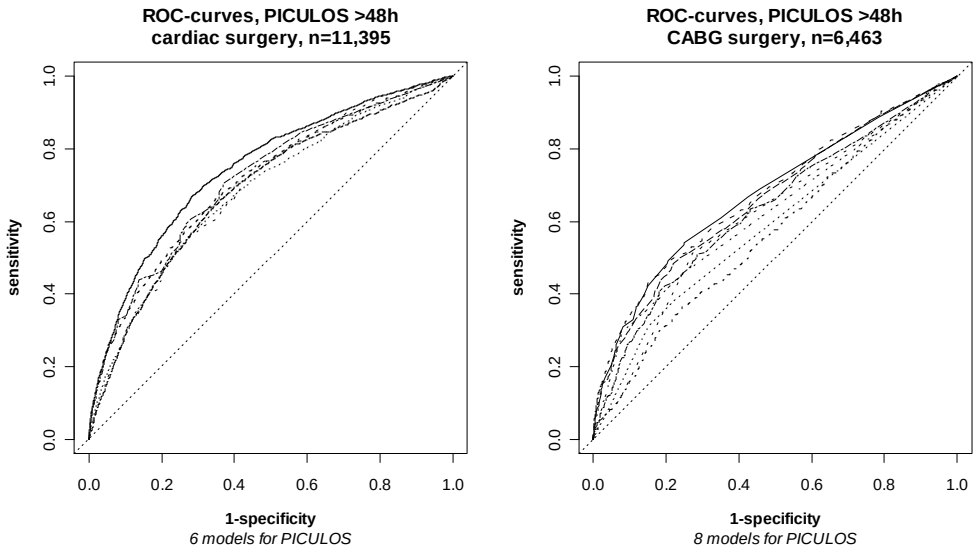


Figure 2 *Receiver operating characteristic (ROC) curves for all 14 prediction models. The diagonal line represents zero discriminative value and corresponds to an AUC of 0.50. ICULOS indicates ICU length of stay.*

We also found considerable differences in AUC between the models for all patients, and the models predicting prolonged ICU stay after isolated CABG procedures. To investigate whether this was due to the models or due to the differences in population characteristics (isolated CABG patients versus all patients), the six models for the general population were also applied to the isolated CABG patients only, resulting again in AUCs varying from 0.55 to 0.69. These AUCs are comparable with the AUCs of the models specially developed for isolated CABG surgery patients. This suggests that it is more complicated to predict prolonged ICU stay in isolated CABG surgery patients than in the cardiac surgery population as a whole, Parsonnet's model and the EuroSCORE showed the best discrimination (0.69 and 0.68 respectively) in the CABG surgery population. Parsonnet's model performed even better than the best-performing model (Wong, 0.68) specially developed for CABG surgery patients only.

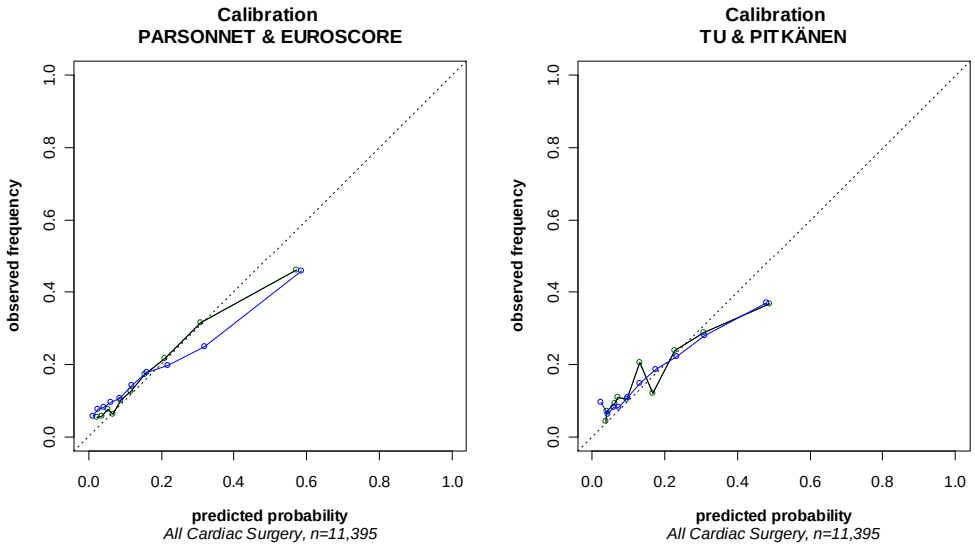


Figure 3A *Calibration plots for models for all cardiac surgery. One plot for the 2 best-performing models (Parsonnet [solid line] and EuroSCORE [dashed line]) and 1 plot for the 2 least-performing models (Tu [solid line] and Pitkänen [dashed line]) are shown. The dotted line represents ideal calibration (with intercept 0 and regression coefficient 1); n=11,395.*

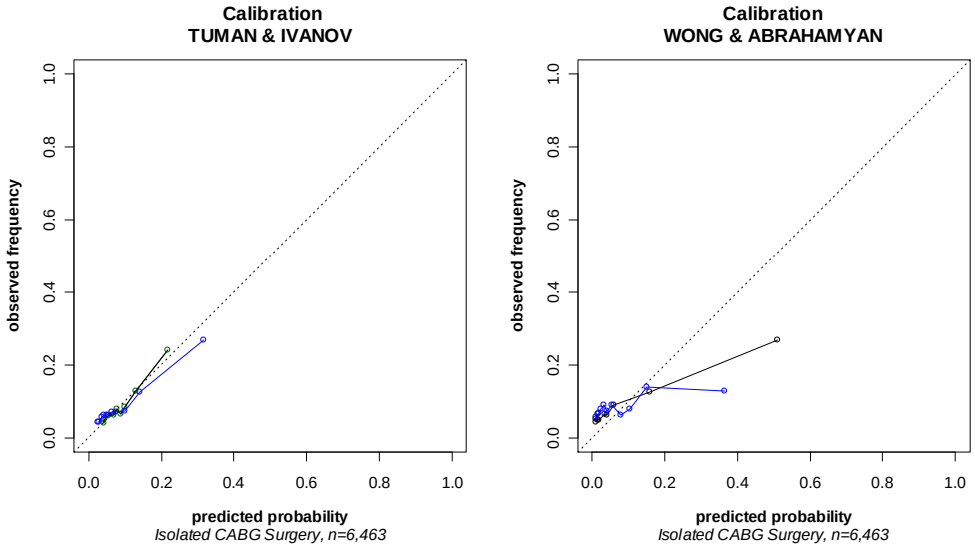


Figure 3B *Calibration plots for models for isolated CABG surgery. One plot for the 2 best-performing models (Tuman [solid line] and Ivanov [dashed line]) and 1 plot for the 2 least-performing models (Wong [solid line] and Abrahamyan [dashed line]) are shown The dotted line represents ideal calibration (with intercept 0 and regression coefficient 1); n=6,463.*

Limitations

Obviously, prolonged ICU stay is intrinsically a continuous variable (length of stay). Accordingly, as with most continuous variables in medicine, one would rather not dichotomise [14] but would rather predict the original length of stay value itself. However, all published models used as outcome dichotomised prolonged stay (length of stay with some threshold value), and our purpose was to validate these models as published.

We made use of a prospective continuous data registry that includes all patients who underwent surgery and systematically recorded a large amount of information on preoperative, perioperative and postoperative characteristics. A disadvantage of using registry data is that not all predictors of the models are available in the registry with exactly the same definition as used to develop these models. We have solved this problem in part by using proxy variables and by replacing missing variables with the incidence or mean of the predictor based on the literature. When too many concessions had to be made before the model could be applied to our data, we excluded the prediction model from this validation study[8,10,12,13,15,25]. Therefore, we do not think that the use of registry data has significantly influenced our conclusions. On the contrary, by using registry data we validated the performance of the models in daily clinical practice, which was specifically the aim of our study.

For most of the variables in the dataset the percentage of missing data was small. For height and weight however, data were missing in 45% of the cases. Deleting 45% of the patient records (doing a complete case analysis) is widely known to yield biased results[32]. We thus applied the best available methods to properly deal with these missing data and minimize this bias and explicitly chose to impute the data by fitting a model[32,50]. With a percentage as high as 45% missing for two variables theoretically multiple imputation is to be preferred over single imputation. However, in the context of multiple imputation it is not straightforward how to estimate the standard errors of part of the performance measures we used in this study. We have performed multiple imputation as a sensitivity analysis, and found similar results for the point estimates, indicating that the numbers presented in this manuscript are not influenced by the choice of the imputation strategy.

We realise that we made use of data from a single centre over a longer time period, which has to be taken into account when generalising our findings.

Conclusions

This extensive quantitative validation study demonstrates that the widely implemented Parsonnet and EuroSCORE models are superior to other models in predicting prolonged ICU stay after cardiac surgery. In current daily practice, Parsonnet's model and the EuroSCORE are widely implemented for the prediction of mortality risk. This allows for the relatively straightforward application of our findings in clinical practice. The predictions that have already been made for mortality can also be used to identify patients with a high probability of prolonged ICU stay. This knowledge, when available prior to surgery, can be used for timely planning of postoperative care and ICU management.

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APPENDIX 1

Query used for the systematic review

The MEDLINE and PreMEDLINE databases were searched for publications concerning prediction models for prolonged ICU stay after cardiac surgery, using the following query:

("Coronary Artery Bypass" OR "Valve surgery" OR "cardiac surgery" OR "cardiovascular surgery" OR "cardiac surgery procedure") AND (algorithm OR "multivariate analysis" OR "logistic model" OR "biological model" OR "statistical model" OR mathematics OR "regression analysis" OR "risk factor" OR "risk assessment" OR "predictive value" OR "Area Under Curve" OR "evaluation study" OR evaluation OR reproducibility OR prediction OR "prediction rule" OR predict OR prognosis OR "prognostic factor") AND (complication OR "adverse event" OR prolonged OR extended) AND stay AND ("intensive care unit" OR ICU).

APPENDIX 2 Table 1a. Methodological features (according to Laupacis[45]) of the six prediction models for PICULOS after *all cardiac surgeries*

	DESCRIPTION OF:	**Parsonnet**	**Tuman**	**Tu**	**EuroSCORE**	**Pitkänen**	**Huijskes**
1	**Reference(s)**	Parsonnet et al. 1989[35]	Tuman et al. 1992[27]	Tu et al. 1994[26]	Nashef et al. 1999[43]; Roques et al. 1999[44]	Pitkänen et al. 2000[21]	Huijskes et al. 2003[17]
2	**Outcome studied**						
	• Definition	Postoperat. mortality	Diff. between pat. with and without morb. *	PICULOS >2 days	Postoperative mortality	PICULOS >2 days	PICULOS >2 days
	• Blind assessment	√	√	√	√	√	√
3	**Predictors**						
	• Definition predictors	√	√	√	√	√	√
	• Number of predictors in model	17	16	10	20	12	14
	• Methods of data collection	Available dataset	Prospective collection	Prospective collection	Prospective collection	Prospective collection	Prospective collection
4	**Patient characteristics**						
	• Data collection time frame	1982 - 1987	n.r.	1990 - 1991	1995	1992 - 1996	1997 - 2001
	• Procedure types	Cardiac surgery	Cardiac surgery	Cardiac surgery	Cardiac surgery	Cardiac surgery	Cardiac surgery
5	**Study site**						
	• No. of centres	1	1	1	132	1	1
	• Region	USA	USA	Canada	Europe	Finland	Netherlands
	• No. of patients in derivation cohort	3,500	3,156	713	13,302	3,061	4,843
6	**Mathematical techniques**						
	• Handling of missing data	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	• Handling of dichotomous, category. and contin. variables	n.r.	n.r.	n.r.	√	√	√

APPENDIX 2 Table 1a. Methodological features (according to Laupacis[45]) of the six prediction models for PICULOS after *all cardiac surgeries*

	DESCRIPTION OF:	Parsonnet	Tuman	Tu	EuroSCORE	Pitkänen	Huijskes
	• Univariable and multivariable Analysis	√	√	√	√	√	√
7	**Results of the model**						
	• AUC	n.r. ‡	n.r.	0.69	0.79 & 0.76†	0.75 & 0.81‖	0.79& 0.78†
	• Calibration plots	√	√	n.r.	n.r.	√	n.r.
	• P-value HL goodness-of-fit	n.r. §	n.r.	0.24	0.4 & 0.68†	0.4 & 0.48‖	0.63& 0.36†
8	**Likelihood of use in practice**						
	• Clinicians perceive items in model as appropriate	√	√	√	√	√	√
	• Risk score	√	n.r.	√	√	n.r.	√
	• Probability of the outcome	√	√	√	√	√	√
	• Model not limited to a risk score, but also suggests a course of action	n.r.	n.r.	√	√	n.r.	n.r.
9	**Previously validated in external cohort**						
	<u>in the initial study</u>						
	• No. of centres	2	1	1	132	1	1
	• Region	USA	USA	Canada	Europe	Finland	Netherlands
	• No. of patients in validation cohort	1,332	394	691	1,479	153 & 82 ‖	2,439
	<u>in an additional study</u>	*For*			*For PICULOS:*		
	• Reference	*PICULOS:* Lawrence et al. 2000[13]	-	Tu et al. 1996[8]	a) Pitkänen et al. 2000[27] b) Pinna Pintor et al. 2003[7]	-	-

APPENDIX 2 Table 1a. Methodological features (according to Laupacis[45]) of the six prediction models for PICULOS after *all cardiac surgeries*

	DESCRIPTION OF:	Parsonnet	Tuman	Tu	EuroSCORE	Pitkänen	Huijskes
	• No. of centres (region)	1 (England)	-	1 (Canada)	c) Nilsson et al. 2004[37] *a) 1 (Finland)* *b) 1 (Italy)* *c) 1 (Sweden)*	-	-
	• No. of patients in the cohort	5,591	-	265	*a) 4,592* *b) 3,404* *c) 488*	-	-
10	**Effects of clinical use measured**	√	n.r.	√	√	n.r.	n.r.

ICU = intensive care unit

n.r. = not reported

AUC = area under the ROC (receiver operating characteristic) curve

HL = Hosmer-Lemeshow (p-value of the Hosmer-Lemeshow goodness-of-fit statistic)

* Difference between two groups: group 1 without morbidity (ICU stay 2.5 ± 0.4 days) and group 2 with morbidity (ICU stay 7.0 ± 9.6 days)

† Figures based on a derivation set and a validation set, respectively

‡ Instead of an AUC for the discriminative ability of the model, a mean correlation (Spearman's rho) was calculated (0.99)

§ Instead of a p-value of the Hosmer-Lemeshow goodness-of-fit statistic for the calibrative ability of the model, a group correlation (Spearman's rho) was calculated (0.85)

|| Figures based on a retrospective dataset and a prospective dataset, respectively

APPENDIX 2 ***Table 1b. Methodological features (according to Laupacis[45]) of the eight prediction models for PICULOS after isolated CABG surgery***

	DESCRIPTION OF:	**Tuman**	**Christakis**	**Wong**	**Ivanov**	**Janssen**	**Abrahamyan**	**Ghotkar**
1	**Reference(s)**	Tuman et al. 1992[27]	**2 models:** Christakis et al. 1996[24]	Wong et al. 1999[23]	Ivanov et al. 1999[22] Ivanov et al. 2000[20]	Janssen et al. 2003[18]	Abrahamyan et al. 2006[16]	Ghotkar et al. 2006[2]
2	**Outcome studied**							
	• Definition	Diff.between pat. with and without morb.	PICULOS >3 days	PICULOS >2 days	PICULOS >2 days	PICULOS≥ 3 days	PICULOS ≥3 days	PICULOS >3 days
	• Blind assessment	* √	√	√	√	√	√	√
3	**Predictors**							
	• Definition predictors	√	√	√	√	√	√	-
	• Number of predictors in model	11	4	9	17	6	4	14
	• Methods of data collection	Prospec-tive	Prospec-tive	Prospec-tive	Prospec-tive	Prospec-tive	Prospec-tive	Prospec-tive
4	**Patient population**							
	• Data collection time frame	n.r.	1990 – 1992	1995	1993 – 2007	2000 – 2001	2003	1997 – 2002
	• Procedure type	CABG	CABG	CABG	CABG	CABG	CABG	CABG
5	**Study site**							
	• No. of centres	1	1	1	2	1	1	1
	• Region	USA	Canada	Canada	Canada	Netherlands	Armenia	England
	• No. of patients in derivation cohort	2,366	889	885	5,354	888	391	5,168

APPENDIX 2 ***Table 1b. Methodological features (according to Laupacis[45]) of the eight prediction models for PICULOS after isolated CABG surgery***

	DESCRIPTION OF:	Tuman	Christakis	Wong	Ivanov	Janssen	Abrahamyan	Ghotkar
6	**Mathematical techniques**							
	• Handling of missing data	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	• Handling of dichotomous, categorical and continuous variables	n.r.	√	√	n.r.	√	n.r.	√
	• Univariable and multivariable analysis	√	√	√	√	√	√	√
7	**Results of the model**							
	• AUC	n.r.	n.r.	n.r.	0.71	n.r.	0.71	0.72 & 0.7†
	• Calibration plots	√	n.r.	n.r.	√	n.r.	n.r.	√
	• P-value HL goodness-of-fit	n.r.	n.r.	n.r.	0.51	n.r.	0.6	0.3 & 0.79†
8	**Likelihood of use in practice**							
	• Clinicians perceive items in model as appropriate	√	√	√	√	√	√	√
	• Risk score	n.r.	n.r.	√	n.r.	n.r.	n.r.	√
	• Probability of the outcome	√	n.r.	√	n.r.	√	n.r.	√
	• Model not limited to a risk score alone, but also suggests a course of action	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

APPENDIX 2 ***Table 1b. Methodological features (according to Laupacis[45]) of the eight prediction models for PICULOS after isolated CABG surgery***

	DESCRIPTION OF:	Tuman	Christakis	Wong	Ivanov	Janssen	Abrahamyan	Ghotkar
9	**Previously validated in external cohort**							
	In the initial study							
	• No. of centres	1	n.r.	-	2	n.r.	n.r.	1
	• Region	USA	n.r.	-	Canada	n.r.	n.r.	England
	• No. of patients in validation cohort	394	n.r.	Bootstrap	2,148	n.r.	n.r.	1,197
	In an additional study							
	• Reference	-	-	-	Ivanov et al. 2000[26]	-	-	-
	• No. of centres	-	-	-	1	-	-	-
	• Region	-	-	-	Canada	-	-	-
	• No. of patients in the cohort	-	-	-	1,904	-	-	-
10	**Effects of clinical use measured**	n.r.	n.r.	n.r.	√	n.r.	n.r.	n.r.

ICU = intensive care unit

CABG = coronary artery bypass grafting

AUC = area under the ROC (receiver operating characteristic) curve

HL = Hosmer-Lemeshow (p-value of the Hosmer-Lemeshow goodness-of-fit statistic, measure of calibrative ability.)

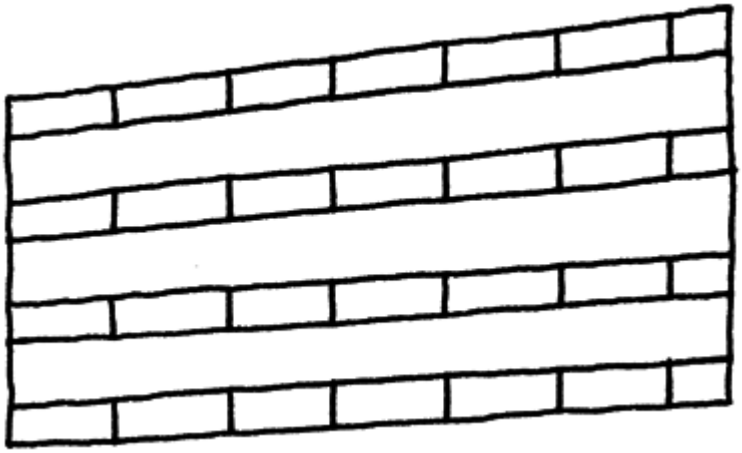
n.r. = not reported

* Difference between two groups: group 1 without morbidity (ICU stay 2.5 ± 0.4 days) and group 2 with morbidity (ICU stay 7.0 ± 9.6 days)

† Figures based on a derivation set and a validation set, respectively

Chapter 2

Predicting prolonged Intensive Care Unit stays in older cardiac surgery patients: a validation study



Ettema RG, Peelen LM, Kalkman CJ,
Nierich AP, Moons KG, Schuurmans MJ.
Intensive Care Medicine 2011;37:1480-7.

ABSTRACT

Purpose: In cardiac surgery prediction models identifying patients at risk of prolonged stay at the Intensive Care Unit (ICU) are used to optimize treatment and use of ICU resources. A recent systematic validation study of 14 of these models identified three models with a good predictive performance across patients of all ages. It is however unclear how these models perform in older patients, who nowadays form a considerable part of this patient population. The current study specifically validates the performance of these three models in older cardiac surgery patients and quantifies how their performance changes with increasing age of patients.

Methods: The Parsonnet model, the EUROSCORE and a model by Huijskes and colleagues were validated using prospectively collected data of 11,395 cardiac surgery patients. Performance of the models was described by discrimination (Area Under the ROC Curve, AUC) and calibration.

Results: For the Parsonnet model, the EuroSCORE and the Huijskes model discrimination clearly decreased with increasing age (AUCs of 0.76, 0.71 and 0.72 for ages 70-75 and 0.72, 0.70 and 0.72 respectively for ages 75-80 and 0.68, 0.64 and 0.69 respectively above 80 yrs). The models showed poor calibration in patients aged >70 (p-values for fit of the models <0.006).

Conclusions: To optimize treatment and ICU resources, risk prediction for prolonged ICU stay after cardiac surgery using the existing models should be done with great care for older patients.

KEYWORDS

Intensive care unit stay; Older People; Cardiac Surgery; Severity-of-illness; Prognosis; Outcome; Validation study

INTRODUCTION

In the last decades, increasingly older, sicker and higher-risk patients have undergone cardiac surgery.[1–4] Older patients, here defined as ≥ 65 years of age, account for almost 60% of cardiac surgical activity [2] and have variable post-surgical outcomes. While non-vulnerable older people have no increased risk of adverse events when compared to the general population[4,5], vulnerable older patients (who are susceptible to physical or emotional injury) are more likely to experience intra- and postoperative events.[6]

In patients undergoing cardiac surgery, preoperative assessment of the risk of these adverse events allows for careful preoperative and postoperative treatment to reduce postoperative morbidity and mortality.[7-11] The predicted risks are also used to optimize management of Intensive Care Unit (ICU) resources. For example, in some hospitals patients with a low risk of adverse events are scheduled for surgery before patients with a high risk[8,12,13] to minimize the probability that high-risk patients disrupt the surgery schedule when they have to stay in the ICU longer than expected. A prolonged ICU stay is a frequently-used approximation of the occurrence of adverse events after cardiac surgery.

To estimate the risk of prolonged ICU stay after cardiac surgery, various models have been developed.[8,13–15,19–22,24-27] However, all of these models were derived from samples that included patients of all ages. Given the aforementioned heterogeneity in outcomes in the older cardiac surgery population, it is likely to be more difficult to correctly identify patients at high or low risk of postoperative events. However, the performance of the existing models in the older population is still unclear. Given the expected increase in the share of older people in Western general populations, from 12.6% in 2000 to 20% by 2030 [2,16,17], it is important to quantify the extent to which the existing models used to predict a prolonged ICU stay after cardiac surgery can be applied to older patients.

In a previous systematic review and validation study, we externally validated fourteen prediction models for prolonged ICU stay after cardiac surgery.[18] We found that the Parsonnet model[19], the EuroSCORE model[20,21], and the model developed by Huijskes and colleagues[22] showed the best performance. However, older patients were clearly underrepresented in these studies. The heterogeneity of older cardiac surgery patients is likely to affect the performance of prediction models. This study therefore focuses specifically on validating the performance of these three prediction models in older patients. In addition, we quantified how the predictive performance of each model changes with the increasing age of patients.

METHODS

Patients

The analysis was performed on a cohort of patients from the Isala Clinics in Zwolle, The Netherlands; this is one of the largest cardiac surgery centers in the Netherlands where over 1,400 cardiac surgery procedures are performed each year. As part of a continuous data registry for patient management, improvement of quality of care and research purposes, pre-, peri-, and postoperative data of all patients undergoing cardiac surgery are collected prospectively. For the current analysis, we used data from all 11,395 procedures conducted between January 1, 2000 and July 31, 2008. Patients gave informed consent for the use of their data for research purposes. All patient identification information was removed before the analyses were conducted.

Age categories

Patient age was calculated by subtracting the date of birth from the date of surgery. In addition, ten age categories were defined: one category included patients aged from 18 to 39 and additional categories were grouped in five-year increments (i.e., 40 to 44 years, 45 to 49 years, etc., up to 75 to 79 years); the last group included all patients who were 80 years and older.

Prediction models

In this study, we compared three prediction models that are all based on logistic regression equations. The Parsonnet model and the EuroSCORE model were originally designed to predict mortality after cardiac surgery but have been used and validated for the prediction of prolonged ICU stay[11,14,15,18,23,24]. Both models are widely implemented in clinical practice. The Parsonnet model includes seventeen predictors and was derived from 3,500 cases between 1982 and 1987 in a single center (New Jersey, USA).[19] The EuroSCORE model was derived from 13,302 surgical cases in 1995 from 132 centers in eight western European countries (Germany, France, United Kingdom, Italy, Spain, Finland, Sweden, and Switzerland); this model includes twenty predictors.[20,21] The model developed by Huijskes and colleagues includes fourteen predictors and was derived from 4,843 cases in a single center in The Netherlands between 1997 and 2001.[22] The Appendix provides a more detailed description of the three prediction models.

Prolonged ICU stay

For each age group, the observed incidence of prolonged ICU stay was calculated. Since there is no consensus on the exact definition of prolonged ICU stay[12], we defined it as an ICU stay of more than 48 hours; this definition was in accordance with the literature[13,15,24-27] and current clinical practice.

Validation of the models in older patients

To quantify the performance of the models, we determined their discrimination and calibration by comparing the actual ICU stay in each patient with the calculated predictions using the original models. The discrimination of a model indicates the extent to which the model distinguishes between patients with and without a prolonged ICU stay. Discrimination was expressed by calculating the areas under the receiver operating characteristic Curves (AUC) with 95% confidence intervals.[28,29] The calibration of a model describes the extent to which the predicted probabilities of a prolonged ICU stay reflect the true probabilities of a prolonged ICU stay. The calibration of a prediction model is influenced by differences between the incidence of the outcome in the original dataset and the validation dataset. To allow for a fair comparison of the models, we adjusted the intercept of each model before applying it to the data, such that for all models the mean predicted probability was equal to the observed outcome frequency.[30,31] We did this for each age category separately. The calibration of the models was judged by means of calibration plots[32,33], by relating the predicted and observed probabilities, and through use of the *U*-statistic (which compares the observed slope and intercept of the calibration plot to the ideal values of 1 and 0, respectively).[37]

Statistical analysis

Missing values occurred in the variables "gender" (0.05%), "myocardial infarction" (0.14%), "serum creatinin" (2.86%), "smoking" (0.13%), "height" and "weight" (together in about 45% of the cases), "NYHA classes" (0.92%), and the outcome variable "ICU length of stay" (1.71%). Single regression and weighted mean imputation techniques were used to substitute for missing values.[33] Both methods are widely known and recommended methods for the substitution of missing values to reduce bias and increase statistical power.[34-38]

In the analyses, first, the relation between age as a continuous variable and the incidence of observed prolonged ICU stay was investigated with a linear regression line through the incidences per age category. The slope of the regression line was tested against a slope of zero (no increase of the incidence of prolonged ICU stay with increasing age). Second, the AUC (with 95% confidence interval) was calculated for each of the three prediction models in all of the above-defined age groups. Linear regression analysis was performed to investigate whether the AUC changed with increasing age; we hypothesized that the AUC would decrease. Finally, calibration plots were constructed for the age categories 70 to 75 years, 75 to 80 years, and 80 years and older, with their accompanying *U*-statistic. Two-sided statistical testing was conducted with a level of significance of 0.05. The statistical package R (version 2.10.1 (2009-12-14), The R Foundation for Statistical Computing) was used for analysis.

Table 1 Baseline characteristics

GENERAL FEATURES		*TYPE OF SURGERY*					*LENGTH OF STAY*		*FRAILTY*		
Age Categories	*Female Gender (%)*	*No. of cases (n)*	*Isolated CABG**	*Isolated Valve**	*Combined**	*other Cardiac Surgery * /***	*ICU Days §*	*Prol. ICU stay */◊*	*Cardiac Surgery in the past*/†*	*Chronic Disease */‡*	*Instable Heart Function */ϕ*
18-39	27.3	172	46 (27)	55 (32)	32 (18)	39 (23)	0.9 (0.8-1.0)	26 (15)	19 (11)	43 (25)	52 (30)
40-44	22.9	235	129 (55)	39 (17)	43 (18)	24 (10)	0.9 (0.8-1.0)	28 (12)	33 (14)	74 (32)	68 (29)
45-49	15.2	449	284 (63)	57 (13)	79 (18)	29 (6)	0.9 (0.8-1.0)	57 (13)	74 (17)	166 (37)	115 (26)
50-54	19.0	816	525 (64)	67 (8)	171 (21)	53 (7)	0.9 (0.8-1.0)	95 (12)	161 (20)	254 (43)	211 (26)
55-59	19.9	1,311	832 (63)	112 (9)	298 (23)	69 (5)	0.9 (0.8-1.0)	163 (12)	215 (16)	649 (50)	311 (24)
60-64	23.0	1,598	987 (62)	160 (10)	399 (25)	52 (3)	0.9 (0.8-1.0)	195 (12)	282 (18)	865 (54)	367 (23)
65-69	28.7	2,060	1,245 (60)	211 (10)	533 (26)	71 (4)	0.9 (0.8-1.1)	303 (15)	364 (18)	1,154 (56)	472 (23)
70-74	33.5	2,262	1,237 (54)	228 (10)	738 (33)	59 (3)	0.9 (0.8-1.6)	409 (18)	377 (17)	1,354 (60)	520 (23)
75-79	41.9	1,790	889 (50)	217 (12)	636 (35)	48 (3)	0.9 (0.8-1.8)	376 (21)	283 (16)	1,116 (62)	394 (22)
≥ 80	49.3	702	289 (41)	104 (15)	293 (42)	16 (2)	1.0 (0.9-2.5)	190 (27)	94 (13)	436 (62)	180 (26)
TOTAL (%)	*29.8*	*11,395 (100)*	*6,463 (56.7)*	*1,250 (11.0)*	*3,222 (28.3)*	*460 (4.0)*	*0.9 (0.8-1.2)*	*1,842 (16.1)*	*1,902 (17.0)*	*6,211 (54.5)*	*2,690 (23.6)*

* n (incidence in %)

** Aorta surgery, surgical correction aneurysm, closing ventricular septal rupture, rhythm surgery

§ median (1st Q, 3rd Q,)

◊ Prolonged ICU-stay is defined as ICU length of stay > 48 hours

† Cardiac surgery in the past: CABG surgery, valve surgery, aortic surgery or percutaneous transluminal coronary angioplasty (PTCA)

‡ Chronic disease including: diabetes, lungdisease, renal or liver function impediment, hypertension or pulmonal hypertension

ϕ Instable heart function: actieve endocarditis, unstable angina, recent.myocardinfarction or surgery indication urgent or emergent

RESULTS

The baseline characteristics of our cohort are depicted in Table 1. The majority of the 11,395 cardiac surgery patients underwent isolated coronary artery bypass grafting (CABG). The proportion of women in the study population increased in patients of 60 years and older (from about 20% before 60 to 50% in the oldest age category of 80 years and older).

The median (IQR) length of ICU stay was 22 (18.7–27.5) hours (Table 1). The first quartile and median value of the ICU stay remains relatively constant over the age categories. Only the third quartile shows a steep increase in the three oldest age categories (Figure 1). The overall incidence of prolonged ICU stay was 16.1% (Table 1); incidences per age category are depicted in Figure 2. The incidence remains fairly constant at around 12% until the age of 65. However, in patients of 65 years and older, the incidence of prolonged ICU stay sharply increased. The slope of the regression line through the incidences was $\beta = 0.0127$ (p-value < 0.008) per year, meaning a significant increase of prolonged ICU stay with increasing age in particular above the age of 64 years (Figure 2).

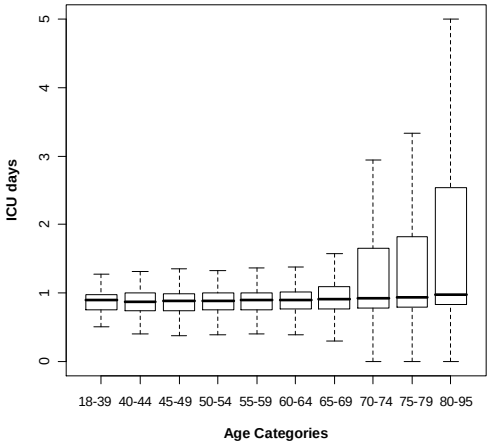


Figure 1 *Length of ICU stay per age category. Five patients (0.22%) in the age category of 70-74, deceased before reaching the ICU, seven patients in the age category of 75-79 (0.39%) and one patient in the oldest age category of 80 years and older (0.14%)*

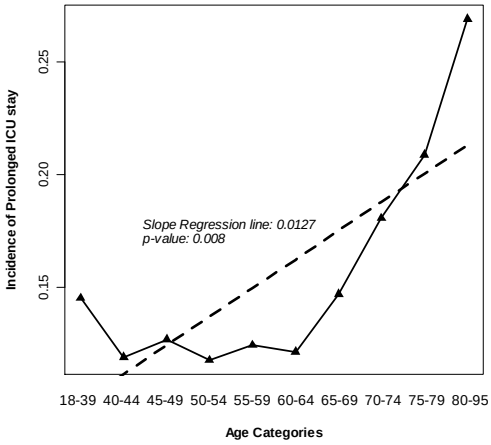


Figure 2 *Incidence of observed prolonged ICU stay (<48 hours) per age category. The dotted line indicates the regression line. A p-value below 0.05 indicates a significant increase in prolonged ICU stay with increasing age*

Figure 3 displays the AUCs with 95% confidence intervals for each age category and each prediction model. The slopes of the fitted linear regression lines were $\beta = -0.012$ ($p = 0.033$), $\beta = -0.014$ ($p < 0.003$), and $\beta = -0.002$ ($p = 0.636$) for the Parsonnet, EuroSCORE, and Huijskes models, respectively.

Table 2 Calibration (U-statistic with p-value) for the three prediction models in three older age categories

	70 to 74 years (n = 2,262)		*75 to 79 years (n = 1,790)*		*80 to 95 years (n = 702)*	
MODEL	***U*-STAT.**	**P-VALUE**	***U*-STAT.**	**P-VALUE**	***U*-STAT.**	**P-VALUE**
Parsonnet	0.91	0.635	10.21	0.006*	31.52	<0.001*
EuroSCORE	11.33	0.003*	17.64	<0.001*	64.45	<0.001*
Huijskes	62.60	<0.001*	61.81	<0.001*	74.15	<0.001*

* p-values <0.05 indicate significantly worse fit of the model.

Figure 4 depicts calibration plots for the three prediction models in each of the three oldest age categories (70 to 74 years, 75 to 79 years, and 80 years and older). Table 2 shows the accompanying *U*-statistics. Both the calibration plot and the *U*-statistic demonstrate that the calibration of all three models for the two oldest age categories is poor. Only the Parsonnet model shows a non-significant *U*-statistic in the age category of 70 to 74 years; this finding is supported by the calibration plot.

DISCUSSION

In this study, we validated the performance of three prediction models for prolonged ICU stay after cardiac surgery in older patients using data from a very large database. We found that the ability of two widely-known models (the Parsonnet and EuroSCORE models) to preoperatively discriminate between high-risk patients and low-risk patients for prolonged ICU stay, reduced considerably with increasing patient age. In patients of 70 to 79 years of age, all three models showed a fair discrimination, ranging between 0.70 and 0.76.

However, in patients of 80 years and older, discrimination drops below 0.70; AUCs of 0.69, 0.68, and 0.64 were observed for the Huijskes, Parsonnet, and EuroSCORE models, respectively. In terms of calibration, none of the three models properly reflected the true probabilities of a prolonged ICU stay in patients of 70 years and older; except for the Parsonnet model which showed a relatively better calibration performance in the age category of 70 to 74 years only.

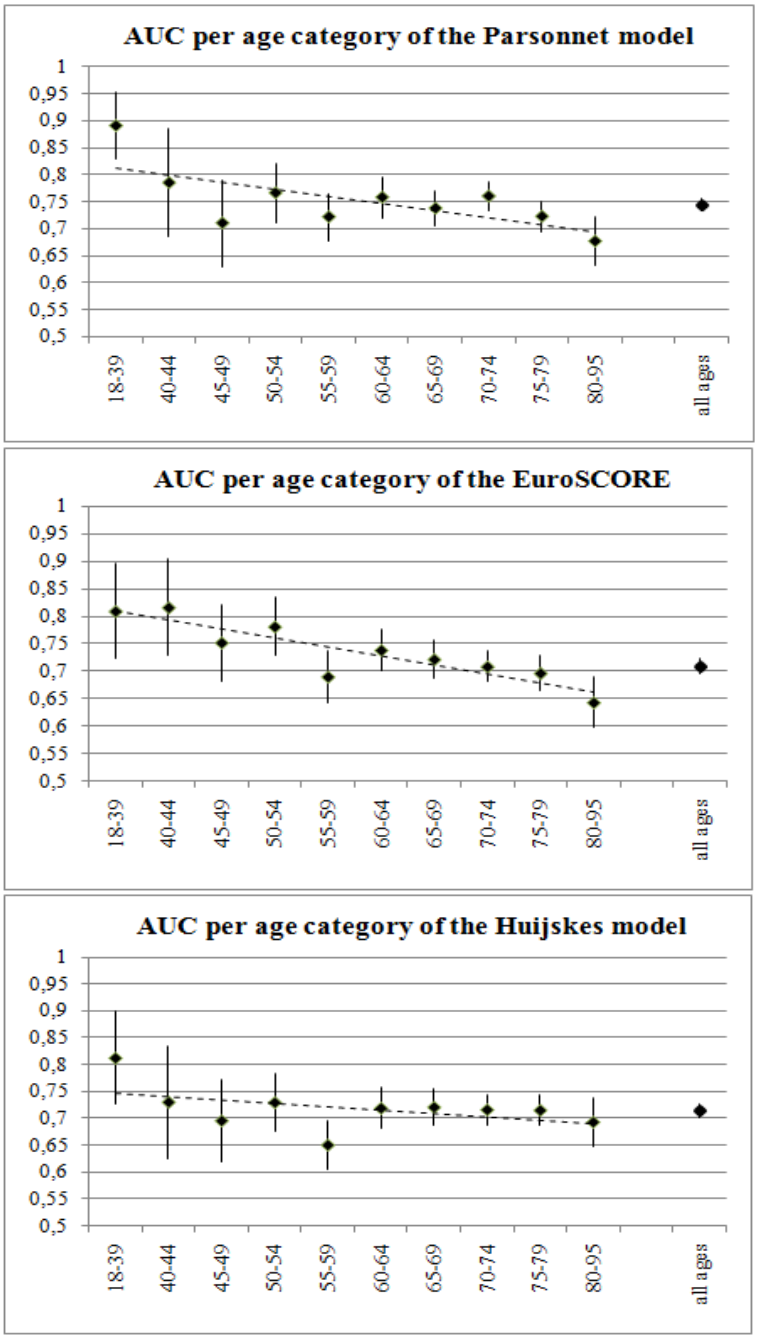


Figure 3 *Areas Under the Curves (AUC) with 95% Confidence Intervals for different age categories and the entire population for the three prediction models. The dotted line indicates the regression line through the AUCs*

Prolonged ICU stay is often used as a proxy for adverse events occurring directly after cardiac surgery. As indicated in the introduction, accurate preoperative assessment of the risk of prolonged ICU stay is used to estimate the complexity of the course of the procedure and the subsequent patient stay at the ICU. Unplanned prolonged ICU stays due to incorrect preoperative prediction leads to an inefficient use of resources.[8,12,13] Although it is theoretically known that one should be careful in applying predictions for individual patients, it is common practice to use scoring systems to preoperatively estimate the risk for the patient on a complicated postoperative course and/or an unfavorable outcome of surgery. However, in order to be able to use the models for these purposes, we have to be sure that the provided probabilities are valid, therefore external validation of prediction models is imperative.[31] Provided the model is well calibrated for the new population, the predicted probability is correct. The difficulty hence lies within the judgment whether the probability is high enough to initiate interventions or low enough to refrain from any actions.

The accurate identification of patients who are likely to experience a particular outcome (e.g., a prolonged ICU stay) is always more complicated in a heterogeneous population.[37,38] We found considerable heterogeneity in the length of ICU stays in patients in the older age categories. The steep increase in the third quartile of ICU stay (Figure 1, top of each box) explains the significant increase in the incidence of prolonged ICU stay with increasing age (Figure 2). As a sensitivity analysis we also fitted a restricted cubic spline regression line, which yielded similar results. This heterogeneity is also reflected in the literature on heterogeneity in the incidence of postoperative adverse events in the older population[4–6,8] and most likely explains the disappointing results in the calibration of the models.

Rowe and Kahn[40] demonstrated in the 1980s that a distinction can be made between "usual aging" and "successful aging," and they recommended that gerontological research incorporates this distinction. Consequently, prediction models for older ICU or surgical patients should incorporate this distinction by, for example, focusing not only on age but also on the patient's frailty, not limited to frailty characteristics in the physical domain of functioning like chronic disease and instable heart function, but also in the social and psychological domains of functioning of the patient, like autonomy, control and cognitive function[40]. Therefore, age is not the only important factor in predicting adverse events; the frailty in the social and psychological domains of functioning of the patient should also be taken into account when making predictions for clinical and critical care.

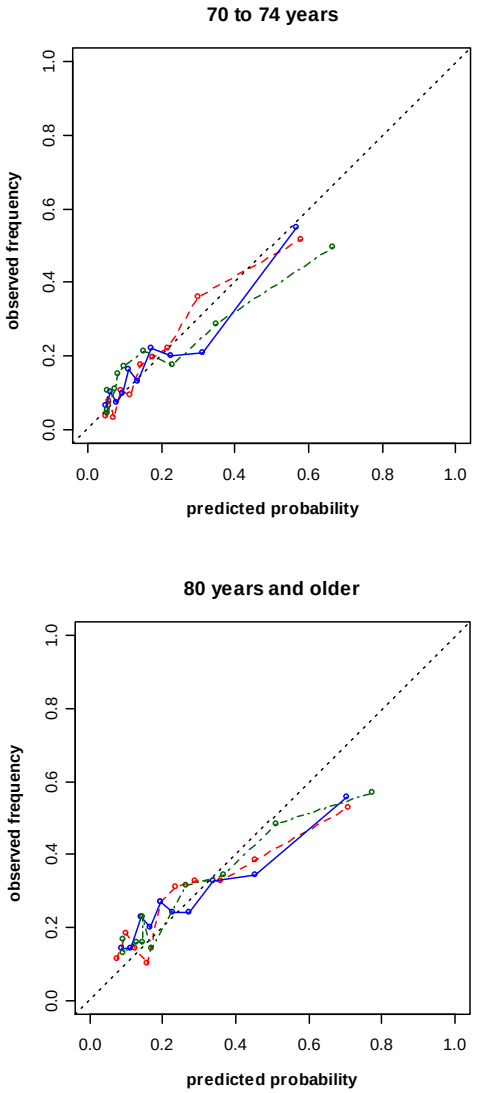


Figure 4 *Calibration plots for the Parsonnet model (dashed line), the EuroSCORE (solid line) and the Huijskes model (dotdashed line) for the three oldest age categories. The diagonal dotted line represents the ideal calibration line with intercept 0 and regression coefficient 1.*

To appreciate the present results, a few additional points must be considered. First different thresholds for a prolonged ICU stay after cardiac surgery are used by others[12], including 24 hours and 72 hours[8,11,14,22,23]. When we repeated the analysis using the thresholds of 24 and 72 hours, the ranking of the models based on their performance did not change. Consequently, the choice of the threshold of 48 hours did not influence the analysis.

Second, we make use of data from a single center over a long time period, which must be considered when generalizing our findings. During the time period of this study a patient was discharged from the ICU when it had achieved the medium care criteria of respiration,

hemodynamics, a positive monitoring of the fast track, temperature, drain production, urine production and consciousness. As a sensitivity analysis we calculated the AUCs of the three prediction models for all ages and the age categories 65 to 69 years, 70 to 74 years and 80 years and older for three time frames (January 2000 – June 2003, July 2003 – December 2005 and January 2006 – July 2008). For all three time frames the AUC's where comparable. Consequently, we do not think the longer time period did influence our findings.

Third, the AUC values we obtained all range between 0.70 and 0.76 for patients of 70 to 79 years of age and between 0.64 and 0.69 for patients of 80 years and older. Although the maximum value for the AUC is theoretically often considered to be 1, in practice this also depends on the difficulty of the prediction problem.[28] As a reference value we developed prediction models on our own data - which would be overfitted by definition- and yielded AUC values ranging from 0.80 to 0.82 (overfitted models) and 0.74 - 0.80 (reduced models). Hence, we believe that the values found for the EuroSCORE, Parsonnet and Huijskes model can be considered fair.

Fourth, for most of the variables in the dataset the percentage of missing data was small. For height and weight however, data were missing in 45% of the patients. Deleting 45% of the patient records (doing a complete case analysis) is widely known to yield biased results.[34,35] We have therefore performed multiple imputation as a sensitivity analysis, and found similar results for the point estimates, indicating that the numbers presented in this manuscript are not influenced by the choice of the imputation strategy.

Finally, to determine the calibration of the models, we explicitly used the *U*-statistic rather than the Hosmer-Lemeshow goodness-of-fit test as the latter is known to have disadvantages when used in relatively large samples.[37] As most researchers are more familiar with the Hosmer-Lemeshow goodness-of-fit test, we repeated the analysis of the calibration of the models using the Hosmer-Lemeshow goodness-of-fit test. This analysis yielded similar results.

Conclusions

Three prediction models to identify patients at increased risk of prolonged ICU stay that have shown to perform well in the general cardiac surgery population show a decreased performance in older patients. This is probably due to the increased heterogeneity among older patients. Therefore, identifying patients at increased risk of prolonged ICU stay after cardiac surgery using one of the three studied models should be performed with great care when older patients are involved. The heterogeneity of the older population should be considered when preselecting patients at high and low risk for a prolonged ICU stay in clinical and critical care.

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APPENDIX

Regression equations and general characteristics of the three prediction models

The Parsonnet model:

1 / (1 + exp(-(-7.032 + 0.054 (age per year) + 0.235 (aortic valve disease) + -0.588 (bypass only) + 0.647 (bypass plus other procedure) + 0.083 (patients treated actively with cholesterol or lipid lowering drugs) + 0.456 (diabetes) + 1.455 (major acute structural damage to the heart) + -0.065 (family history) + 0.509 (female gender) + 0.263 (hypertension (<140/90 mm HG) + -0.553 (left ventricular aneurism, resected) + 0.271 (left ventricular ejection fraction ≤50%) + 0.542 (left ventricular ejection fraction ≤30% & >50%) + 0.813 (left ventricular ejection fraction <30%) + 0.835 (mitral valve disease) + -0.271 obesity (≥1.5x ideal weight*) + 1.473 (preoperative intra-aortic balloon pump) + 0.893 (reoperation) + 0.089 (smoking))))

**) ideal weight was calculated by the "Metropolitan Life" tables of height and weight*

The EuroSCORE:

1 / (1 + exp(-(-4.789594 + 0.095 (age per year) + 0.336 (female gender) + 0.642 (serum creatinine >200 µmol/L) + 0.642 (extra cardiac arteriopathy*) + 0.470 (long-term use of bronchodilators and steroids) + 0.833 (neurological dysfunction severely affecting ambulation or day-to-day functioning) + 0.956 (previous cardiac surgery) + 0.470 (myocardial infarction within 3 months before operation) + 0.405 (left ventricular ejection fraction 30-50%) + 0.916 (left ventricular ejection fraction <30%) + 0.405 (chronic or episodic peripheral edema, pleural effusion or hepatomegaly) + 0.693 (systolic pulmonary pressure >60) + 0.916 (active endocarditis, patient under antibiotic treatment) + 0.405 (unstable angina, requiring intravenous nitrates) + 0.470 (urgent operation) + 1.030 (emergency surgery) + 0.788 (critical preoperative state) + 1.335 (ventricular septal rupture) + 0.470 (non-coronary surgery) + 1.163 (thoracic aortic surgery))))

**) extra cardiac arteriopathy, defined as the presence of one or more of the following risks: present intermittent claudication; carotid disease (unilateral or bilateral, occlusion or >50% stenosis); previous surgery for vascular disease (abdominal aorta, limb arteries or carotids); planned surgery of the abdominal aorta, for vascular limb, arteries or carotids*

The model developed by Huijskes and colleagues:

1 / (1 + exp(-(-4.8 + 0.34 (age per 5 years over 60) + 0.51 (female gender) + 0.52 (history of transient ischemic attack or cerebrovascular accident) + 1.15 (creatinin level (150–200) + 2.3 (creatinin level (>200) + 0.26 (hemoglobin (>90%, 80–90%, <80% of the lower normal limit per gender) + 0.97 (left ventricular ejection fraction <30%) + 0.72 (pulmonary artery pressure >50 mmHg) + 0.96 (prior cardiac surgery, 1, 2 or more) + 0.97 (myocardial infarction in last 24 h) + 0.74 (failed percutaneous coronary intervention) + 0.91 (emergency procedure) + 0.82 (critical preoperative state derived from EuroSCORE) + 0.58 (combined coronary artery bypass graft /aortic valve procedure) + 1.68 (combined coronary artery bypass graft /mitral valve procedure))))

Regression equations and general characteristics of the three prediction models

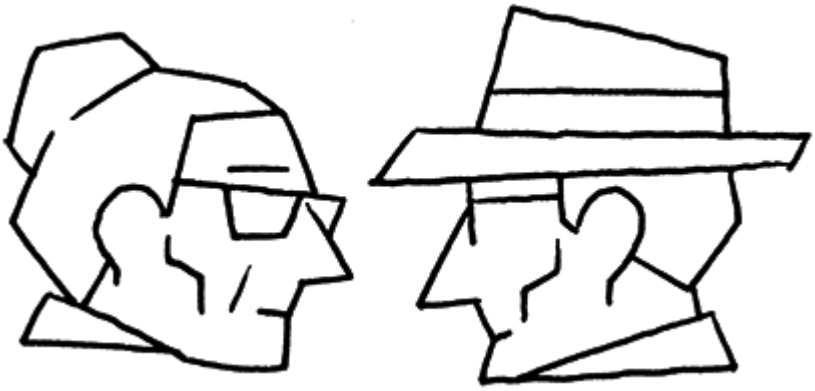
	PARSONNET* [24]	EUROSCORE** [24,25]	HUIJSKES [26]
Year of publication	1989	1999	2003
Period of data collection	1982-1987	1995	1997-2001
Region (number of centers)	USA(1)	Europe(132)	Netherlands(1)
No. of subjects in deriv. set	3,500	13,302	4,843
No. of predictors	17	20	14

* Originally developed for mortality, validated for Prolonged ICU Length Of Stay (PICULOS) by Hsieh et al. 2007 [14]; Ettema et al 2010 [18] and Lawrence et al. 2000 [23].

** Originally developed for mortality, validated for PICULOS by Pinna Pintor et al. 2003 [11]; Nilsson et al. 2004 [15]; Ettema et al 2010 [18] and Pitkänen et al. 2000 [24].

Chapter 3

Identifying older cardiac surgery patients at risk of postoperative delirium, depression, pressure ulcer and infection using preadmission data



Ettema RG, Schuurmans MJ, Hoogendoorn ME, Nierich AP, Kalkman CJ, Moons KG, Peelen LM.
Submitted

ABSTRACT

Background/Objectives: Timely identification of patients at risk for relevant and frequent postoperative hospital complications in older cardiac surgery patients allows for adequate preoperative preparation. Patient characteristics known before hospital admission that are predictive for frequently occurring postoperative complications were investigated.

Design: In a prospective cohort study in 1,761 cardiac surgery patients of 65 years or older physical and psychosocial predictors were collected. Multivariable regression models were developed based on these variables to predict postoperative delirium, depression, pressure ulcer and infection. Taking into account the concept of the multifactorial geriatric syndrome we also developed a model for the combined outcome.

Setting: Elective cardiac surgery

Participants: Older patients scheduled for cardiac surgery

Intervention: Identification of patients at risk

Measurements: Postoperative delirium, depression, pressure ulcer, hospital infection, and potential predictors measured before hospital admission.

Results: Preadmission characteristics associated with postoperative delirium, were the EuroSCORE, age, history of CVA or TIA, benzodiazepines, a walking stick or walker, and being dependent on informal care. Female gender, benzodiazepines, deafness, and insoles were related to postoperative depression. Patient characteristics associated with postoperative pressure ulcer were the EuroSCORE, history of tricuspid insufficiency, fraxiparin, increased serum creatinin level, living alone, and being physically disabled. The EuroSCORE, history of tricuspid insufficiency and diuretics were associated with postoperative infection.

Conclusions: We identified groups of predictors for common postoperative complications in older cardiac surgery patients and found that these outcomes are best predicted separately. As these predictors are known before admission, patients with increased risk can be selected timely for more intensive evaluation and preparation to reduce their risk.

KEYWORDS

Frailty; Older People; Cardiac Surgery; Identification; Postoperative Complications

INTRODUCTION

Nowadays, older patients, here defined as ≥65 years of age, account for almost 60% of the procedures in cardiac surgery. It is known that post-surgical outcomes in these patients vary considerably.[1–4] Vital older cardiac surgery patients have little increased risk of complications of hospitalization.[5,6] In contrast, frail older cardiac surgery patients are more likely to experience in-hospital complications.[1,7] These patients frequently suffer from postoperative delirium (incidence 14.7% to 46.0%)[8,9], depression (10.0% to 37.7%)[10,11], pressure ulcer (14.0% to 18%)[12,13] and nosocomial infection (8.3% to 54.5%)[14-17] These complications are in turn associated with functional and cognitive decline and decrease in quality of life (QoL) and wellbeing after discharge.[18,19]

Timely identification and selection of patients at risk of those complications would allow for better preoperative preparation to optimize the condition of the patient and reduce the probability of an unfavorable outcome.[20-24] Currently, the risk of a complicated postoperative course is estimated based on clinical variables measured *during* hospital admission, using approximate outcomes such as risk of prolonged stay at the Intensive Care Unit (ICU) or death.[20,22,23] In a previous study we found that the performance of these models is disappointing in older patients.[23]

In order to allow for timely preparation, identification and selection of high-risk patients should be improved [22,23] and is to take place at least two weeks before surgery.[24-25] In this manuscript we used data from a large cohort to investigate which risk factors can identify older patients who develop postoperative complications after cardiac surgery, using variables that are available before hospital admission. Because we expected to find predictive patient characteristics especially in the psychosocial domain of functioning of the patient, not only clinical but also social and psychological aspects of the patient's condition were taken into account.

Many older patients scheduled for cardiac surgery present with multiple comorbid health problems. As in older people multiple risk factors are thought to be related to multiple outcomes – the so-called multifactorial geriatric syndrome [20,26,27] – we did not only develop four separate models for the outcomes delirium, depression, pressure ulcer and infection, but also a model for the combined outcome ('any of these complications').

METHODS

Patient population and candidate predictors

For this analysis we used a prospective cohort of patients from the Isala Clinics in Zwolle, The Netherlands; this is one of the largest cardiac surgery centers in the Netherlands where over 1,400 cardiac surgery procedures are performed each year.

In this clinic, pre-, peri-, and postoperative data of all patients undergoing cardiac surgery are prospectively collected as part of a continuous data registry for patient management, improvement of quality of care, and research.

We reviewed the literature to identify candidate predictors describing physical, psychological and social aspects of preadmission functioning of the patient associated with postoperative delirium, depression, pressure ulcer or infection.[18,28-31] It should be noted that because our purpose is risk assessment, these associations do not need to be causal.[32] Variables that were not already part of the continuous data registry were added to the preadmission screening with a questionnaire. This preadmission screening, including the added questionnaire, was filled out by the patient approximately 30 days before surgery. An overview of all candidate predictors included in this study is presented in the Appendix.

We used data from all 1,761 procedures in patients of 65 years and older conducted between January 1, 2008 and October 30, 2010 where patients had given informed consent for use of their data. The local ethical review board approved the study protocol. All patient identifying information was removed before the analyses were conducted.

Outcomes

All four outcomes were collected throughout the entire postoperative part of hospital admission. Delirium was measured using the Delirium Observation Screening Scale.[33] Depression was measured using the Geriatric Depression Screening Scale.[34] Patients were screened for delirium and depression one to three days after surgery during medium care stay, and during the discharge procedure. Pressure ulcer was diagnosed by daily physical inspection through nurses, following the International NPUAP-EPUAP Pressure Ulcer Classification System[35], where all measurements of stage I (non-blanchable redness of intact skin) and higher were considered as pressure ulcer. Hospital infection was diagnosed based on laboratory testing. We conducted an additional analysis to identify the independently contributing predictors for the occurrence of 'any of these complications'.

Missing values

Missing values occurred in 26 candidate predictors (ranging from 0.3% to 1.8% in patient characteristics which are regularly used in clinical practice, and from 24.8% to 44.6% in variables that were added to the preadmission screening) and in three outcome variables (infection (2%), delirium (23.3%), and depression (26.1%)). Missing values were substituted through multiple imputation, a widely known method for the substitution of missing values to reduce bias and increase statistical power.[36,37] We used five imputation sets, performing the statistical analysis on each dataset and pooling the statistical results using Rubin's rule.[38]

Table 1 Characteristics of the study population in the physical, and psychosocial domains of functioning

n=1,761	***No. of patients***	***Incidence %***
General		
Age, median (1stQ - 3rdQ)	74.9	69.9-78.2
EuroSCORE, median (1stQ - 3rdQ)	6	5-8
Female Gender	649	36.9
Physical Condition		
Previous MI	278	15.8
Hypertension	902	51.2
Diabetes	453	25.7
Type 1	104	5.9
Type 2	349	19.8
COPD	270	15.3
CVA or TIA	164	9.4
Psychological Condition		
Anxious for the Surgery	787	44.7
Anxious for the Anesthesia	541	30.1
Depression	222	12.6
Socio Economic Condition		
Living alone	284	16.1
Depending on Informal Care	225	12.8
Level of Education†		
Low	998	56.7
Mediate	509	28.9
High	254	14.4
Type of surgery		
Isolated CABG	847	48.1
Isolated Valve	245	13.9
Combined CABG-Valve	296	16.8
Other cardiac surgery‡	373	21.2
Postoperative complications		
Delirium	315	17.9
Depression	262	14.9
Pressure Ulcer	193	11.0
Infection	132	7.5

If else, median (1stQ - 3rdQ) is indicated; EuroSCORE= European System for Cardiac Operative Risk Evaluation; COPD = Chronic Obstructive Pulmonary Disease; CVA = Cerebral Vascular Accident; TIA = Transient Ischemic Attack; CABG = Coronary Artery Bypass Surgery

† Education level: low = Elementary, Lower Vocational, Domestic Science; mediate = Lower General Secondary, Intermediate Vocational, Higher General Secondary, High School; high = Higher Vocational, University

‡ Rhythm Surgery, Aorta Ascendance Replacement, Aortic Root Replacement, Correction Aneurysm Left Ventricle, Aortic Arch Surgery

Table 2 The associated preadmission patient characteristics* per section for each of the five outcomes

Sections	***Delirium†***	***Depression†***	***Pressure Ulcer†***	***Infection†***	***Any complication†/‡***
General	-age -diabetes	-female -diabetes -MI-days -BMI	-diabetes -serum creatinin -BMI	-	-age -diabetes -MI-days
History	-mitral insufficiency -aorta stenosis -renal failure -CVA/TIA -chronic lung disease	-main stem stenosis -mitral stenosis -stomach problems	-tricuspid insufficiency -PTCA -renal failure	-tricuspid insufficiency -extra cardiac vessel pathology	-tricuspid insufficiency -aorta stenosis -renal failure -CVA/TIA -chronic lung disease
Frailty	-EuroSCORE -wants information on surgery & anesth.	-EuroSCORE -wants information on surgery & anesth.	-EuroSCORE -preoperative depression	-EuroSCORE	-EuroSCORE -wants information on surgery & anesthesia
Medication	-use of: beta blockers; benzodiazepines; diuretics; cordaron	-use of: beta blockers; benzodiazepines; diuretics	-use of: fraxiparin; diuretics; lipid lowering drug	-use of: beta blockers; diuretics; plavix	-use of: beta blockers; benzodiazepines; diuretics; Ca-antag.; nitrates; lipid lowering drug
Condition	-low LVEF	-	-low LVEF	-low LVEF -IABP	-low LVEF
Resources	-use of stick/walker -deafness	-use of insole, -deafness	-use of stick/walker -physical disabled	-use of stick/walker -use of a brace -use of orthopedic shoes	-use of stick/walker -deafness

Table 2 The associated preadmission patient characteristics* per section for each of the five outcomes

Sections	***Delirium†***	***Depression†***	***Pressure Ulcer†***	***Infection†***	***Any complication†/‡***
Social status	-rest on informal care -contacts are mainly with fellow believers	-number of visits	-living alone	-	-rest on informal care -contacts are mainly with fellow believers
Economic Status	-level of education -stress in work	-level of education -stress in work	-level of education	-level of education	-level of education -stress in work

* All patient characteristics are measured in the preadmission period approximately 30 days before the surgery

† All associations are pooled from the five imputed datasets

‡ One model predicting postoperative Delirium and/or Depression and/or Pressure Ulcer and/or Infection

MI-days = number of days between a myocardial infarction and the cardiac surgery procedure; BMI = Body Mass Index (kg/m^2); CVA = Cerebral Vascular Accident; TIA = Transient Ischemic Attack; PTCA = Percutaneous Transluminal Coronary Angioplasty; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = Left Ventricle Ejection Fraction; IABP = Intra-Aortic Balloon Pump

Predictor selection

Given the large number of potential predictors, we used a stepwise approach for predictor selection, based on clinical knowledge and regression analysis. First, based on clinical knowledge[32,37] we grouped candidate predictors into eight sections: General, Comorbidity, Resources, Social status, Economic Status, Frailty (chronic reduction in physical or mental condition), Medication and Condition (recent reduction in physical condition). Second, we used regression analysis to reduce the number of predictors in the models. For each of the outcomes separately we first fitted multivariable logistic regression models within each section, selecting important predictors per section with backward elimination using Akaike's information criterion as a threshold.[37]. Then, again for each outcome separately, we combined the important predictors from each of the sections into a full multivariable regression model and again used stepwise backward selection to arrive at small (final) models (which are considered the final models throughout this manuscript).Continuous variables were fitted with restricted cubic splines.

Performance of the models

The performance of the models was expressed in terms of accuracy, discrimination and calibration. Accuracy was calculated as the Yates slope (difference between the mean predicted probabilities for the patients with and without the particular postoperative complication), and the Brier score (quadratic difference between predicted probability and actual outcome (0 or 1) for each patient).[39] The *discrimination*, the extent to which the model is able to distinguish patients with high risk of the complication from patients with low risk, was estimated by Receiver Operating Characteristic (ROC) curves and the accompanying C-statistic with a 95% confidence interval.[40] The *calibration*, the extent to which the model accurately predicts risk, was judged by calibration plots[41] and the *U*-statistic.[40] To prevent overfitting of the final models, bootstrap (n=1000) resampling validations were done.[37] The statistical package R (version 2.14.1 (2011-12-22), The R Foundation for Statistical Computing) was used for all analyses.

RESULTS

Patient characteristics

Table 1 shows the baseline characteristics of the patient population. In total, 640 patients (36%) experienced one or more of the four postoperative complications, the majority of which (n = 490/28%) suffered from one complication. One hundred and ten patients (6%) suffered from two complications, 36 (2%) of three complications and only 4 patients (0.2%) experienced all four complications after their surgery.

Predictive factors

Table 2 shows the patient characteristics within the eight sections that showed the strongest association with each of the five outcomes. These patient characteristics were then used in the full models. The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), the use of diuretics, and level of education, were associated with all outcomes. With regard to patient history, cardiac problems were most associated. With regard to resources, the use of a walking stick or a walker was most associated with the outcomes. Next to the use of diuretics, with respect to medication, the use of beta blockers was most associated and the use of benzodiazepines was especially associated with the occurrence of postoperative delirium and depression.

Combining the predictors from these sections and reducing the models, yields the final models as depicted in Table 3. From the total of sixteen predictors which remained in the final models, six of them originated from the added questionnaire, of which four are physical patient characteristics (use of a walking stick or walker, deafness, use of insoles, physical disabled) and two are social patient characteristics (depending on informal care and living alone). The logistic EuroSCORE remains significant for prediction of delirium, pressure ulcer and infection. The use of benzodiazepines remains in both the models for the prediction of delirium and depression. Tricuspid insufficiency in patient's history remains in both the models for the prediction of pressure ulcer and infection. All other predictors are associated with only one of the four postoperative complications.

Table 3 also shows the performance measures. Highest Yates slopes and highest discrimination were found for the model predicting delirium. The C-statistics of the models ranged from 0.72 (95% CI: 0.69-0.75) for delirium to 0.59 (0.55-0.62) for the model predicting depression.

Discrimination of the model for any complication was in between these with values for the C-statistic of 0.65 (0.63-0.68). Figure 1 depicts the calibration plots. The model predicting postoperative depression showed a small range of predicted probabilities and considerable variation in observed incidence of the lower range of predicted probabilities. The plots for the other models indicate a good calibration throughout the range of predicted probabilities.

Table 3 Predictive factors for each outcome: final models, with their performance statistics

	DELIRIUM		DEPRESSION		PRESSURE ULCER		INFECTION		ANY COMPLICATION‡	
Preadmission predictors*	***Coef.†***	***P val.†***	***Coef.†***	***P val.†***	***Coef.†***	***P val.†***	***Coef.†***	***P val.†***	***Coef.†***	***P val.†***
Uses walking stick/walker	0.537	0.0009							0.696	0.000
Depends on informal care	0.492	0.0046								
Age per year	0.070	0.0000							0.036	0.000
History of CVA or TIA	0.520	0.0093								
Use of Benzodiazepines	0.368	0.0306	0.364	0.0216					0.414	0.004
Deafness			0.446	0.0097					0.381	0.007
Use of insoles			1.048	0.0010						
Female gender			0.316	0.0216						
Physical disabled					0.525	0.0035				
Living alone					0.447	0.0196				
Serum creatinin µmol/L§					0.002	0.0388				
Use of Fraxiparin					0.371	0.0383				
Logistic EuroSCORE‖	2.300	0.0000			1.765	0.0003	1.840	0.0005	1.288	0.002
History of tricuspid insufficiency					0.767	0.0004	0.732	0.0033	0.525	0.003
Use of diuretics							0.489	0.0090		
History of Renal Failure									0.381	0.030
(Intercept)	*-7.348*		*-2.043*		*-2.954*		*-3.053*		*-3.617*	

Table 3 Predictive factors for each outcome: final models, with their performance statistics

	DELIRIUM	DEPRESSION	PRESSURE ULCER	INFECTION	ANY COMPLICATION‡
Performance statistics¶					
Calibration					
U-statistic (p-value)	0.0000 (1)	0.0000 (1)	3.615 (0.164)	0.0000 (1)	0.0587(0.971)
Accuracy					
Yates Slope	0.088	0.018	0.057	0.022	0.069
Brier Score	0.135	0.124	0.093	0.068	0.220
Brier Scaled	0.059	0.069	0.084	0.134	0.033
Discrimination					
C-statistic	0.72	0.59	0.68	0.64	0.65
(95%CI)	(0.69-0.75)	(0.55-0.62)	(0.63-0.72)	(0.58-0.69)	(0.63-0.68)

* All patient characteristics are measured in the preadmission period approximately 30 days before the surgery

† All statistics are pooled from the five imputed datasets, using Rubin's Rule [38]

‡ One model predicting postoperative Delirium and/or Depression and/or Pressure Ulcer and/or Infection

§ Reference for normal values range for female 50-110 μmol/L and for male 60-120 μmol/L

‖ Reference for a normal value for the Logistic EuroSCORE <0.2

¶ All performance statistics are scaled from 0 to 1. Higher Yates' slope as well as lower Brier Scores and higher Brier Scaled and higher discrimination (AUC) C-statistics and non-significant p-values of the calibration *U*-statistic, represent better performance.

CVA= Cerebral Vascular Accident; TIA = Transient Ischemic Attack; EuroSCORE = European System for Cardiac Operative Risk Evaluation, AUC = Area Under the (Receiver Operator Characteristic) Curve; C-statistic = Concordance-statistic (measure for discrimination ability of a model); *U*-statistic = Unbiased-statistic (measure for calibration ability of a model)

DISCUSSION

With our study, which includes 1,761 older cardiac surgery patients, we identified patient characteristics measured four weeks before surgery that are associated with the common postoperative complications delirium, depression, pressure ulcer, and infection. We used patient characteristics related to physical, psychological and social functioning measured in the preadmission period. This provides a more extensive base for the predictions which can be utilized in the waiting time before the hospital admission with cardiac surgery, to identify and select patients at increased risk of postoperative complications and to allow for optimizing the condition of patients.

This perspective of risk assessment in the preadmission period is not very common. In the literature, most studies focus on the hospital period itself and studies show differences in evidence on preoperative prediction of the occurrence of postoperative complications. In comparing our results with models developed for in hospital use in predicting delirium, depression and infection, we found similarities and differences with respect to important predictors.

For instance, in predicting delirium in a sample of 122 cardiac surgery patients, the Mini Mental State Examination, prior stroke or TIA, albumin: $\leq$3.5 or $\geq$4.5g/dL and the Geriatric Depression Scale were identified as preoperative in-hospital predictors[42] Our final model for delirium also included prior stroke or TIA as a predictor.

In a study in 141 cardiac surgery patients on preoperative characteristics measured one day before surgery, female gender, higher state anxiety, and less social support were found to be predictive of postoperative depression. In this study depression was measured using the Center for Epidemiological Studies Depression Scale (CES-D), the State-Trait Anxiety Inventory (STAI), and the Perceived Social Support Scale (PSSS).[43] In our model for predicting depression, we also found female gender as a predictor and the use of benzodiazepines, which could be a marker for higher state anxiety.

In a study including 809 CABG surgery patients, deep sternal wound infection or mediastinitis was predicted with the preoperatively measured EuroSCORE and the preoperative Society of Thoracic Surgeons (STS) risk score.[44] Our model for postoperative in-hospital infection also includes the EuroSCORE, together with a history of tricuspid insufficiency and the use of diuretics. Feuchtinger and colleagues reviewed the literature for predictors for pressure ulcer and found older age, oxygen-supply diseases, and low albumin level as important parameters for developing pressure ulcers in cardiac surgery patients.[45] In our prediction model for pressure ulcer these characteristics were not included.

In general, identification of patients at risk of postoperative complications using only information available up to four weeks before surgery is complicated by the fact that the course of the surgical procedure and the admission to the intensive care unit are in between.

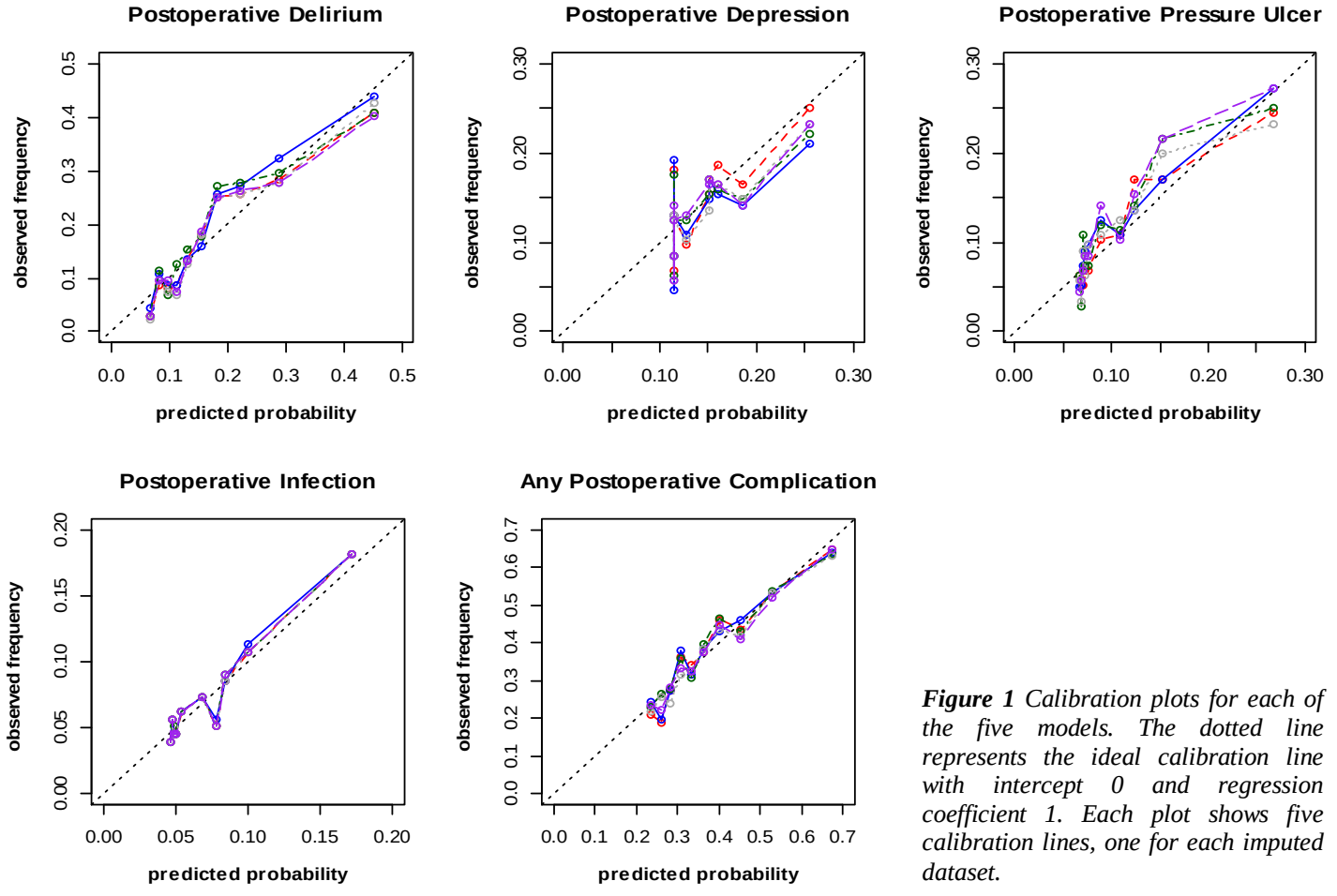


Figure 1 *Calibration plots for each of the five models. The dotted line represents the ideal calibration line with intercept 0 and regression coefficient 1. Each plot shows five calibration lines, one for each imputed dataset.*

Nevertheless, in this study we were able to identify these predictive patient characteristics for identifying and selecting patients, providing for timely and adequate preoperative preparation and in this way prevent for overtreatment.

To fully appreciate the present results some additional points must be considered. First, in our study the outcomes delirium and depression are screened with screening instruments and the two outcomes pressure ulcer and infection are diagnosed. In clinical practice delirium is difficult to diagnose in these patients and depression cannot be diagnosed during the admission period, because according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) the symptoms have to last six weeks.

Therefore, for these two outcomes we have chosen to use validated instruments for screening, which are also often used in practice. Using screening instruments instead of actual diagnoses makes it more difficult to discriminate between patients with and without the disease; hence, we expect that this has led to an underestimation of the discriminative power of the predictors found for postoperative delirium and depression.

Second, for most of the variables in the data were no missing values. However considerable amount of missing values occurred in some patient characteristics that are not commonly used in clinical practice, which are mainly in the psychological and social domain of functioning of the patient. We applied the best available methods to properly deal with these missing data and minimize bias, by using multiple imputation.[36-38]

Third, for the selection of patient characteristics we distinguished eight sections, based on clinical knowledge. This might have erroneously included or excluded candidate predictors for further selection. As a sensitivity analysis we therefore also performed factor analysis for variable reduction.[46] Although the distribution of the predictors over the factors slightly differed from the distribution among the sections, the same variables were found to have the most predictive ability.

Finally, we realize that we made use of data from a single center, which must be taken into account when generalizing our findings.

Conclusion

In this study we identified predictors for postoperative complications in older cardiac surgery patients that are known before admission and combined them in five compact prediction models. These predictors mainly relate to the physical preoperative condition of the patient. In contrast to the geriatric paradigm, where multiple factors are thought to be related to multiple outcomes, prediction of those complications is best done using separate sets of predictors. Based on these predictors, patients at increased risk of postoperative complications can be timely identified and selected to allow for preoperative optimization of the patient´s condition.

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APPENDIX

All preadmission patient variables considered as potential predictors of postoperative complications (% missings)	
Section 'General' ***(from the hospital continuous data registry)***	
1. Gender (0)	2. Diabetes type 1 and type 2 (1.4)
3. Age (0)	4. Serum creatinine (1.6)
5. Number of days between MI and Surgery (0)	6. BMI (1.3)
Section 'Comorbidity (*from the hospital continuous data registry)*	
7. Instable Angina (0)	8. Aorta Insufficiency (0)
9. Hypertension (0)	10. Aorta Stenosis (0)
11. PTCA (0)	12. Mitral Insufficiency (0)
13. Main Stem Stenosis (0)	14. Mitral Stenosis (0)
15. Tricuspid Insufficiency (0)	16. Pulmonary Hypertension (0)
17. Cardiac Surgery (0)	18. Extra Cardiac Vessel Pathology (0)
19. Coronary Surgery (0)	20. Renal Failure (0)
21. Valve Surgery (0)	22. Hypothyroidism (0)
23. Stomach problems (0)	24. Chronic Lung disease (0)
25. Hyperthyroidism (0)	26. CVA or TIA (0.9)
Section 'Resources' ***(from the added questionnaire)***	
27. Glasses, Contact lenses (29.1)	28. Orthopedic Shoes (32.1)
29. Hearing Aid (31.3)	30. Walking stick or Walker (31.6)
31. Wheelchair (32.0)	32. Deafness (31.6)
33. Means, such as: Insoles, Corset, Support Stocking, Stair Lift, Mobility Scooter (31.7)	
Section 'Economic Status'*(from the added questionnaire)*	
34. Level of education (30.1)	35. Finished education (37.5)
36. Stressful deadlines in professional live (42.4)	37. Freedom to organize own work (43.0)
38. Standing of sitting in professional live (43.0)	39. Heavy physical work (41.1)
Section 'Frailty' ***(added questionnaire)***	
40. Logistic EuroSCORE (0.3) *(derived from data registry)*	41. Preoperative Depression (24.8)
42. Anxious for the Surgery or Anesthesia (34.6)	43. Wants information about the Surg. and Anesth. (44.6)
44. Physical disabled (31.5)	

Section 'social' ***(derived from the added questionnaire)***	
45. Actively Supported (29.9)	46. Depending on Informal Care (30.9)
47. Residential status: such as: Living alone, Widow(er), Live together (31.0)	48. If religious, contacts are mainly with fellow believers (32.0)
49. Number of weekly visits received or paid (33.6)	
Section 'Preadmission Medication' ***(derived from the hospital continuous data registry)***	
50. Ascal (0)	51. Ca-Antagonist (0)
52. Beta Blockers (0)	53. Benzodiazepines (0)
54. Plavix (0)	55. Lipide lowering drug (0)
56. Gastric Juice Inhibitor (0)	57. Nitrates (0)
58. Cholesterol lowering drug (0)	59. RAAS Inhibitor (0)
60. Pulmonic Medication (0)	61. Heparine for 24 hours (0)
62. Diuretics (0)	63. Digoxin (0)
64. Fraxiparin (0)	65. Cordaron (0)
66. NSAID (0)	67. Steroids (0)
68. Coumarin (0)	69. Thyrax (0)
70. Insulin (0)	71. Oral Antidiabetics (0)
Section 'Condition' ***(derived from the hospital continuous data registry)***	
72. Artificial Respiration (0)	73. IABP (0)
74. Inotropics (0)	75. Anuria or Oliguria, less than 10ml per hour (0)
76. Ventricular Tachycardia or Fibrillation, Cardiopulmonary Resuscitation (0)	77. Low LVEF (1.8)

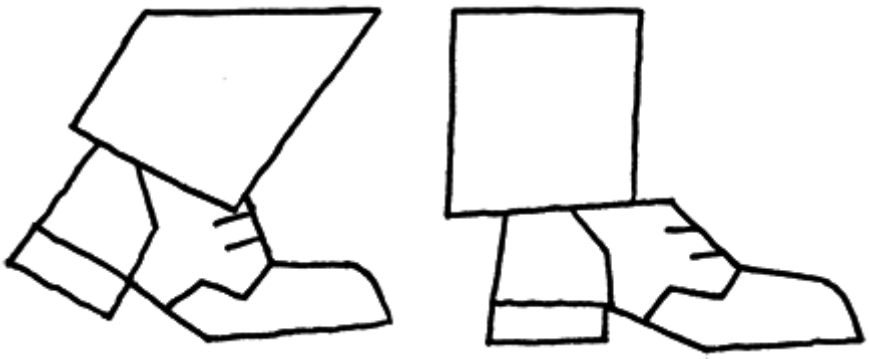
BMI = Body Mass Index (kg/m2); PTCA = Percutaneous Transluminal Coronary Angioplasty; CVA= Cerebral Vascular Accident; TIA = Transient Ischemic Attack; EuroSCORE = European System for Cardiac Operative Risk Evaluation; RAAS = Renin Angiotensin Aldosterone System; NSAID = Non-Steroidal Anti-Inflammatory Drugs; IABP = Intra-Aortic Balloon Pump; LVEF = Left Ventricle Ejection Fraction; Frailty: chronic reduction in physical or mental condition; Condition: recent reduction in physical condition

Part 2

Preadmission preparation of older patients

Chapter 4

Preadmission interventions to prevent postoperative complications in older cardiac surgery patients: A systematic review of the literature



Ettema RG, Koeven van H, Peelen LM, Kalkman CJ, Schuurmans MJ.
The International Journal of Nursing Studies, 2014 Feb;51(2):251-60.

ABSTRACT

Objective(s): The literature on postoperative complications in cardiac surgery patients shows high incidences of postoperative complications such as delirium, depression, pressure ulcer, infection, pulmonary complications and atrial fibrillation. These complications are associated with functional and cognitive decline and a decrease in the quality of life after discharge. Several studies attempted to prevent one or more postoperative complications by preoperative interventions. Here we provide a comprehensive overview of both single and multiple component preadmission interventions designed to prevent postoperative complications.

Methods: We systematically reviewed the literature following the PRISMA statement guidelines.

Results: Of 1,335 initial citations, 31 were subjected to critical appraisal. Finally, 23 studies were included, of which we derived a list of interventions that can be applied in the preadmission period to effectively reduce postoperative depression, infection, pulmonary complications, atrial fibrillation, prolonged intensive care unit stay and hospital stay in older elective cardiac surgery patients. No high quality studies were found describing effective interventions to prevent postoperative delirium. We did not find studies specifically targeting the prevention of pressure ulcers in this patient population.

Conclusions: Multi-component approaches that include different single interventions have the strongest effect in preventing postoperative depression, pulmonary complications, prolonged intensive care unit stay and hospital stay. Postoperative infection can be best prevented by disinfection with chlorhexidine combined with immune-enhancing nutritional supplements. Atrial fibrillation might be prevented by ingestion of N-3 polyunsaturated fatty acids. High quality studies are urgently needed to evaluate preadmission preventive strategies to reduce postoperative delirium or pressure ulcers in older elective cardiac surgery patients.

KEYWORDS

Cardiac surgical procedure; Preadmission preventive measures; Postoperative complications; Older patients

INTRODUCTION

Over the recent decades, the patient population undergoing cardiac surgery has become older, sicker and higher-risk.[1-3] Patients of 65 years and older account for almost 60% of cardiac surgeries [3] and show substantial heterogeneity in postoperative outcomes (Ettema et al., 2011). Whereas some older people have little increased risk of adverse events compared to the general population[4,5] vulnerable older patients (who are susceptible to physical or emotional injury) are more likely to experience adverse intra- and postoperative events.[6,7]

The reported incidence of postoperative complications after cardiac surgery patients is high: ranging from 17% to 43.1% for delirium[8,9]; from 17.5% to 28.7% for depression[11,12]; from 14.3% to 18% for pressure ulcer[12,13]; from 10.6% to 54.5% for hospital infection[14-17]; from 10.6% - 12.1% for postoperative pulmonary complications[18-20] and from 15.2% to 33.3% for atrial fibrillation[21]. These complications are associated with functional and cognitive decline and a decrease in quality of life and well-being after discharge[9,22].

Already in the nineties, Recker[23] concluded that preoperative teaching might facilitate admission of the cardiac surgical patient on the day of surgery, which could shorten the length of hospital stay. Other attempts have been made to prepare patients for cardiac surgery in the preadmission[24-27] in order to prevent adverse events in the postoperative period. Many common and comorbid health problems, particularly in older persons, are multifactorial in etiology. These multifactorial syndromes are health conditions in which more than one risk factor is related to the outcome.[28,29] A good example of a multifactorial geriatric syndrome is delirium, which results from a complex and dynamic interplay between the various risk factors in a vulnerable patient. An effective intervention should therefore properly address this multifactorial origin.[29] Also, due to the multifactorial origin of syndromes more postoperative complications can occur at the same time in one vulnerable patient and risk factors are often related to more complications.[28]

However, in the literature several interventions that showed evidence of effectiveness aimed at preventing a single adverse outcome[14-16,19,21] while others reported effectiveness of a combined multifactorial approach targeted at preventing multiple adverse outcomes simultaneously.[28-31] As a consequence, it is still unclear how older cardiac surgery patients can best be prepared for their cardiac surgery.

Therefore, the purpose of the present systematic review is to provide an overview of both single and multi-component preadmission interventions designed to prevent single and multiple postoperative complications in older elective cardiac surgery patients.

METHODS

We used the PRISMA statement recommendations in the design, literature search, analysis, and reporting of our systematic review.[32]

Search strategy

In a first round, two authors (RE, HvK) independently searched for studies that satisfied the inclusion criteria. In a second round, also reference lists of identified articles were studied for relevant studies which were not revealed in the first round. This snowball technique was primarily performed by one of the authors (HvK). Studies were included if they examined patients scheduled for elective cardiac surgery, who underwent a preoperative intervention aimed to prevent postoperative adverse events, complications or prolonged length of hospital stay. The exact search query and the accompanied electronic search strategy using the PICO framework[33], is presented in Appendix 1. Searches were performed using the MEDLINE, EMBASE, Cochrane, Cinahl and PsychINFO databases for the period from January 1980 to March 2011.

The primary outcome assessed was the effectiveness of a preoperative intervention in preventing a postoperative complication, i.e. a decreased incidence of delirium, depression, pressure ulcer, infection, postoperative pulmonary complication or atrial fibrillation in the intervention group. We also assessed length of hospital stay as a secondary outcome, as a prolonged hospital stay could indicate a complicated postoperative hospital course.

Every effort was made to obtain the full text of all relevant papers. The two first authors (RE, HvK) individually read each of these articles and summarized the results in an Excel file for subsequent analysis.

Inclusion and exclusion criteria

Studies were included if they compared a preoperative or combined pre- and postoperative intervention with standard care, namely randomized clinical trials or cohort studies. The patients were undergoing elective cardiac surgery with required postoperative hospitalization and had a mean or median age of at least 60 years, because a sample with a mean age of 60 will include substantial numbers of much older people. The intervention aimed to prevent postoperative complications or adverse events during hospitalization or prolonged length of hospital stay. Because certain drugs possibly have a preventive effect, medication studies were included, although dose response studies were excluded.

Furthermore, because we searched for studies describing preventive interventions compared with standard care, studies were excluded if they focused on preventive interventions that are already part of standard care, such as heparin for prevention of deep vein thrombosis. Because we focused on patient oriented interventions applicable in the preadmission period only, studies of interventions related to management and education of hospital staff were excluded as well. After scanning the title and abstract, studies that did

not present data on outcomes related to the prevention of postoperative complications or adverse events were discarded.

Quality assessment

We included randomized controlled trails as well as cohort studies. The quality of the studies was independently assessed by two reviewers (RE, HvK), using the Dutch versions of the Cochrane Collaboration randomized clinical trials tool and the cohort study tool.[34] All discussions and disagreements were settled in meetings between the two reviewers. An overview of the assessment criteria, both for randomized clinical trials and cohort studies, is depicted in appendix 2.

The methodological quality of each appraised article was graded using the UK National Health Service and the Dutch Institute for Healthcare Improvement[35,36] ratings of A, B, C and D (See table 1 for further explanation). Because we focused on comparative studies, only articles with grades of A or B were selected for our analyses.

Table 1 Levels of methodological quality[35,36]

LEVEL	EXPLANATION
A1	Systematic review of at least two independently conducted studies of A2 level
A2	Randomized double-blind comparative clinical studies of good quality and sufficient size
B	Comparative studies but not with all the features listed under A2
C	Non-comparative studies
D	Expert opinion

RESULTS

After removing the duplicates, the database searches and the additional snowball search resulted in 1,335 citations. In screening on domain and inclusion criteria, 1,304 articles were excluded. In 689 studies, also patients who underwent other surgery were included and no distinction was made to cardiac surgery patients only and in 214 studies the main intervention was not in cardiac surgery patients. In 175 studies patients with a mean age younger than 60 years were included and in 162 studies the age of included patients was not provided. In 60 studies the intervention was not defined and four studies focused on dose response relation only. Finally, 31 articles remained.

The articles then were subjected to a critical appraisal, and 22 randomized clinical trials and one cohort study of preventive interventions for older cardiac surgery patients were selected (see figure 1). Methodological reasons for excluding eight articles were unclear randomization in seven studies, no blinding (none of the three: patient, caregiver

and researcher) in seven studies, five studies were underpowered and in one study there was no description of the outcomes.

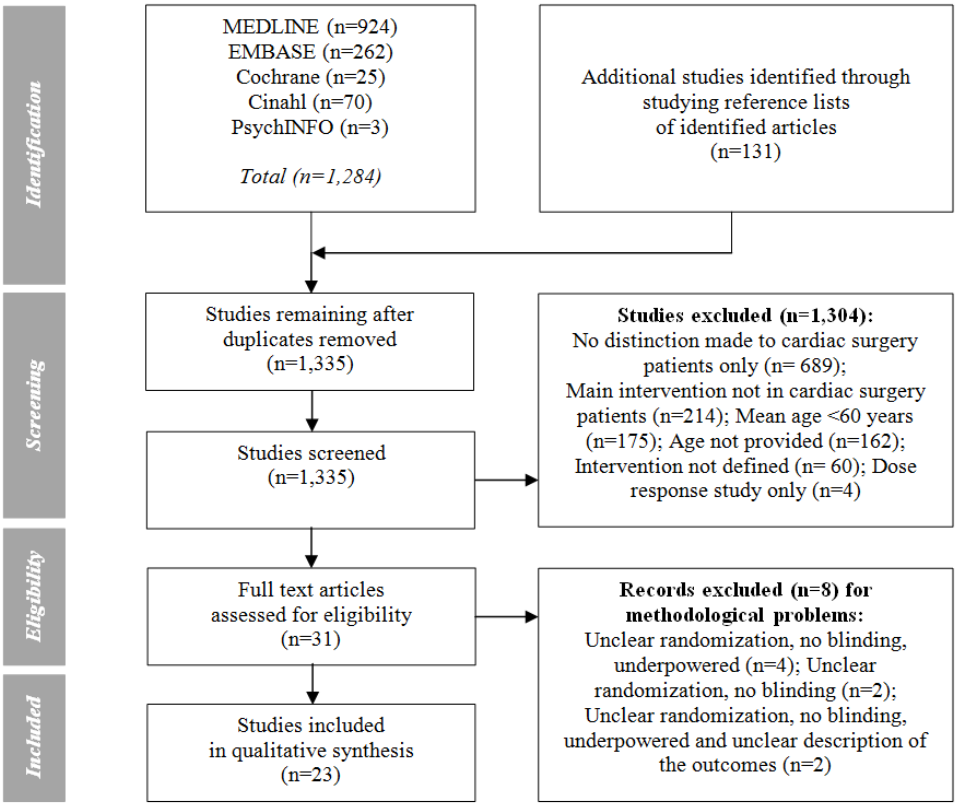


Figure 1 *Flowchart of the search and review process according to the PRISMA guideline*

Finally, nine of the included studies[8,14,15-17,19,27,30] were of high quality (quality level A2) and the remaining fourteen studies were of fair quality (quality level B).[21,37-49] Appendix 2 represents an overview of the methodological aspects of the 23 included studies. Table 2 describes the included studies. The sample size of the 23 selected studies ranged from 45 to 991 patients. The studies included different types of interventions, including combined (multi component) and single component interventions targeting both single and multiple complications. Twelve studies were designed to prevent a single adverse outcome and eleven studies were designed targeting multiple adverse outcomes.

Furthermore, in seventeen articles a single component intervention was studied and in only six articles a multi component intervention was studied. An overview of the identified single and multi-component interventions targeting single and multiple complications is shown table 3.

In high-quality studies (quality level A2), a reduction in hospital infections[14,15], postoperative pulmonary complications[19], depression[30], general practitioner visits[30], anxiety and pain[31] was found. Additionally, these studies found an increase in postoperative physical activity.[30] In fair quality studies (quality level B), interventions were identified that achieved a reduction in the occurrence of the following: depression[41-44]; atrial fibrillation[21]; postoperative pulmonary complications[49]; length of hospital stay[37,42,43,45]; length of intensive care unit stay[37,45]; high blood pressure[39,41,42,47]; high cholesterol and, high BMI[42,47]; anger, fatigue, confusion and reduced vigor[44]; anxiety[40,42,43,47]; high heart rate and pain[41,44]; tension[41]; and cigarette smoking.[47] Furthermore, these studies examined interventions that increased physical activity[47] and quality of live.[37,42,47]

Some interventions were applied only in the pre-operative period, and some were applied both preoperatively and postoperatively. The beginning of the intervention periods varied from nine months before surgery to one day before surgery. The ending of the intervention periods varied from before admission to after surgery at the time of hospital discharge. Furthermore, application of the interventions varied from monthly to a single event prior to the operation.

Thirteen interventions were designed for patients undergoing isolated coronary artery bypass grafting surgery, one for patients undergoing off-pump coronary artery bypass grafting surgery, seven for patients undergoing general cardiac surgery (including heart-valve surgery), one for cardiac surgery patients with chronic kidney disease, and one study of high-risk patients undergoing cardiac surgery.

In seven studies, the intervention demonstrated no effect at all (see tables 2 and 3). In the remaining sixteen studies the interventions under study showed a significant reduction in postoperative complications (see table 2). A more complete overview of the included studies is given in appendix 3. An overview of all outcomes is presented in appendix 4.

Within the included studies, research was done on the prevention of depression, atrial fibrillation, postoperative pulmonary complications and prolonged length of hospital stay for patients who underwent coronary artery bypass grafting surgery. In patients who underwent a general cardiac surgery procedure, the prevention of delirium, depression and confusion, nosocomial infections, postoperative kidney failure, prolonged length of hospital stay and quality of live were evaluated. No studies of high quality were found that described effective interventions to prevent postoperative delirium. No studies were found that examined the prevention of pressure ulcers in older cardiac surgery patients.

Table 2 Summary data from 23 studies

AUTHOR, YEAR (REF.) (DESIGN)	TYPE OF SURGERY (SAMPLE SIZE)	INTERVENTION	POSTOPERATIVE OUTCOME	EFFECT & EFFECT SIZE	STUDY QUALITY
Arthur, 2000 [37] (RCT)	CABG (146)	Individualized supervised exercise training twice weekly for eight weeks and monthly nurse-initiated telephone calls	Prolonged ICU stay, prolonged LOS, decrease in QoL	Significant decrease in ICU stay (median diff. 1.5h) and LOS (med diff. 1d) and significant increase in Qol physical component (mean diff.3 points); no effect in QoL mental component	B+
Bay, 2008 [38] (RCT)	CABG (166)	Five chaplain visits focusing on positive and negative religious coping items, preoperatively during admission	Anxiety, depression, hopelessness	No effects found	B-
Brasher, 2003 (RCT)	Cardiac Surgery (230)	Omission of deep breathing exercises at each physiotherapy visit preoperatively preoperative during admission	Early postoperative mobilization	No effect found	B
Calò,2005 [21] (RCT)	CABG (160)	N-3 polyunsaturated fatty acids for a minimum of five days preoperatively until hospital discharge	Atrial fibrillation	Significant reduction in both atrial fibrillation (risk diff 0.19) and LOS (mean diff. 0.9d)	B-
DeRiso, 1996 [14] (RCT)	Cardiac surgery (353)	0.12% chlorhexidine gluconate (CHX) oral solution, for 30 seconds twice daily preoperatively until ICU discharge	Oropharyngeal decontamination and nosocomial infections	Significant reduction of infections (risk diff 0.09) infected patients and mean diff. 18) and accompanied antibiotic prescription (reduc. 55%)	A2
Furze, 2009 [30] (RCT)	CABG (204)	HeartOp Program: Cognitive-behavioral 45–60 minute first interview eight weeks before surgery, followed by ten to fifteen minute phone calls to the patient at home at weeks one, three and six and monthly until admission	Postoperative physical activity, depression and GP visits	Significant decrease in depression (reduction 11.7 points), clasp mobility (reduc 0.95 points) and cardiac beliefs (reduc 3.5 points); no effects found in reduction of GP visits	A2
Gamberini, 2009 [8] RCT)	Cardiac Surgery (120)	Prophylactic short-term administration of oral rivastigmine, a cholinesterase inhibitor: 1.5 mg of oral rivastigmine daily, before surgery until six days post-surgery	Postoperative delirium, haloperidol and Lorazepam use, ICU-stay and LOS	No effect found	A2

Table 2 Summary data from 23 studies

AUTHOR, YEAR (REF.) (DESIGN)	TYPE OF SURGERY (SAMPLE SIZE)	INTERVENTION	POSTOPERATIVE OUTCOME	EFFECT & EFFECT SIZE	STUDY QUALITY
Garbossa, 2009 [40] (RCT)	CABG (51)	Physiotherapeutic instructions on ventilatory exercises, from 24 hours before surgery until hospital admission	Anxiety	Significant reduction of anxiety with preop. Physioth (mean diff 3.8 points); postop physioth. not effect.	B
Goodman, 2008 [42] (RCT)	CABG (188)	Nurse-led programme of support and lifestyle counseling and preparation for surgery at monthly intervals	High BP, high Cholesterol, high BMI, anxiety, depression, prolonged LOS and reduced QoL	Significantly less decrease in the QoL physical component (mean diff.2.9 points); no effects on BP, HDL Chol, BMI, anxiety, depression, LOS or the QoL mental component	B+
Hulzebos, 2006 [19] (RCT)	CABG (279)	Preoperative assessment and risk stratification and individualized, tailored inspiratory muscle training (IMT) seven times a week, for at least two weeks before surgery	Postoperative pulmonary complications	Significant reduction in LOS (median diff. 1d), PPC grades 1(median diff. 25 points), 2 (med. diff. 4p) and 3 (med. diff. 14p) and pneumonia (med. diff. 13p)	A2
Kshettry, 2006 [41] (RCT)	Cardiac Surgery (104)	Preoperative relaxation skills training with guided imagery and a 30-minute gentle touch or light massage (e.g., music, massage, and guided imagery) and postoperative treatment	High heart rate, high BP, pain and tension	Significant reduction in pain and tension (mean diff.1.1 points day 1; mean diff.0.9 points day 2); HR and BP did not decrease	B-
Ku, 2002 [43] (RCT)	CABG (60)	Individual instruction in progressive exercises and daily activities, and exercise, and a daily activities programme during hospitalization	Anxiety and LOS	Anxiety was significantly reduced (mean diff 9.8 points); LOS did not decrease	B-
Leserman, 1989 [44] (RCT)	Cardiac Surgery (27)	Twice a day training in eliciting the relaxation response before and after surgery	High BP and HR, low relaxation response, tension, depression, anger, fatigue, confusion and reduced vigor	Significant decrease of tension (mean diff before and after 1.8 points) and anger (0.5p); no reduction of BP, HR, relaxation response, depression, fatigue, vigor and confusion	B-
Mahler, 1998 (RCT)	CABG (257)	Three experimental videotapes involving different approaches for preparing CABG patients for surgery and the in-hospital recovery period evenings prior to surgery	Prolonged ICU stay and prolonged LOS	Significant reduction in ICU stay (mean diff 0.06–2.03 days).and LOS (0.07-2.98)	B-

Table 2 Summary data from 23 studies

AUTHOR, YEAR (REF.) (DESIGN)	TYPE OF SURGERY (SAMPLE SIZE)	INTERVENTION	POSTOPERATIVE OUTCOME	EFFECT & EFFECT SIZE	STUDY QUALITY
Marathias, 2006 [46] (RCT)	Cardiac Surg. with Chronic Kidney Disease (45)	Intravenous hydration for twelve hours prior to surgery	Low peri- and postoperative outcomes: MI, arrhythmia, CPB time, aortic cross-clamp time, duration of surgery, length of intubation, ICU stay, use of IABP, LOS, hospital death	No effects found	B
McHugh, 2001 [47] (RCT)	CABG (98)	Health education and motivational interviews, monthly, according to individual need; in patients' homes	Anxiety, depression, cigarette smoking, high BMI, high BP, decrease in physical activity and decrease in QoL	Significant decrease in cigarette smoking (risk diff 0.33), BMI (mean reduc 1 point), seven day recall activity (mean reduc 152 minutes), plasma cholesterol (mean reduc 0.5 mmol/l), BP (syst reduc 12.7 and diast 13.1 mmHg), and significant improvement in QoL	B-
Segers, 2008 [15] (RCT)	Cardiac Surgery (991)	Chlorhexidine mouth wash (10 ml) four times daily; and nasal gel four times daily in both nostrils, from admission to one day post-surg.	Hospital infections	Significant reduction of nosocomial infections (risk diff 0.11) and LOS (mean diff 6.7d)	A2
Shuldham, 2002 [31] (RCT)	CABG (356)	Four hours of education early in the waiting period for admission	Postoperative pain, anxiety, depression, prolonged LOS and decreased general well-being	No effect found	A2
Stiller, 1994 [48] (RCT)	CABG (120)	*Intervention 1)* No chest physiotherapy during admission *Intervention 2)* Preoperative physiotherapy four times daily on the first two postoperative days and twice daily on the third and fourth postoperative days	Postoperative pulmonary complications	No effect found	B

Table 2 Summary data from 23 studies

AUTHOR, YEAR (REF.) (DESIGN)	TYPE OF SURGERY (SAMPLE SIZE)	INTERVENTION	POSTOPERATIVE OUTCOME	EFFECT & EFFECT SIZE	STUDY QUALITY
Tepaske, 2001 [16] (RCT)	Cardiac Surgery (45)	Preoperative oral immune-enhancing nutritional supplement for five days to ten days before the operation	Hospital infections	Sign. reduction in infection(s) (risk diff 0.36), and pneumonia (risk diff 0.29); no reduction was found in urinary tract and wound infections	A2
Tepaske, 2007 [17] (RCT)	High-Risk Cardiac Surgery (70)	*Intervention 1)* Glycine-enriched immune-enhancing formula *Intervention 2)* Standard preoperative immune-enhancing-formula Both starting five to ten days preoperatively	Postoperative complications, low nutrition status, and infection	No effects found	A2
Watt-Watson, 2004 [27] (RCT)	CABG (406)	Preadmission education two to seven days prior to surgery, standard care and pain booklet group focused on communicating pain and the use of analgesics during admission	Pain measured by analgesic prescription and administration	No effects found	A2
Yánez-Brage, 2009 [49] (Cohort)	Off-pump CABG (263)	Respiratory physiotherapy the morning after admission and the morning after surgery	Postoperative pulmonary complications	Significant reduction in atelectasis (risk diff 0.19); no reduction in other PPCs	B

CABG = Coronary Artery Bypass Grafting surgery procedure, LOS = Length Of Hospital stay, ICU = Intensive Care Unit, QoL = Quality of Live, BP = Blood Pressure,
HDL Chol. =High Density Lipoprotein Cholesterol, HR = Heart Rate, BMI = Body Mass Index (kg/m2), PPCs = Postoperative Pulmonary Complications, IABP = Intra-Aortic Balloon Pump, MI = Myocardial Infarction

DISCUSSION

In this systematic review we identified a series of single and multi-component preadmission interventions that have been shown with a sufficient level of evidence to reduce single and multiple postoperative complications in older patients undergoing elective cardiac surgery. The susceptibility for these complications is related to the vulnerability of older cardiac surgery patients due to multifactorial geriatric syndromes.[28,29]

Only one of the 23 studies in our systematic review was aimed at delirium. This was done within a multi outcome setting, e.g. intensive care unit-stay and length of hospital stay, using a single pharmacological intervention: oral rivastigmine. Unfortunately no effect was found. Also in medication studies in other surgery populations, no effect was found after low-dose haloperidol[50] or donepezil[51] in elective orthopedic surgery patients. Notwithstanding that a patient experiencing a delirium will also benefit from a single pharmacologic treatment, evidence for a possible ability of preventive medication in decreasing the incidence of delirium in older patients after surgery, is still lacking.

Six studies in our systematic review were aimed to target depression, from which five studies within a multi complication setting. The interventions were mainly relaxation, education, exercise, motivational interview and lifestyle counseling. Similar results in preventing depression were found in older patients after hip fracture surgery[52] and older patients with breast cancer after hip fracture surgery.[53]

In our systematic review we did not find studies on preoperative interventions targeting postoperative pressure ulcer in older cardiac surgery patients, neither did we find such studies in other surgical domains. This is probably due to the nature of pressure ulcers. The causes of pressure sores are mechanical pressure, shear and frictional forces on the skin and underlying tissue. Risk factors that could be targeted in a multi component approach are neuropathy, nutrition deficiency, moist skin and infection.[54]

Four studies in our systematic review were targeted postoperative pulmonary complications as a single complication. The interventions were nutritional supplementation and respiratory physiotherapy. We did not find studies concerning preventive interventions in other populations applicable in the preadmission period. In a review, Pelosi and Jaber[55] found evidence for perioperative noninvasive respiratory support deceasing atelectasis formation.

Only one study was aimed at prevention of atrial fibrillation as a single complication, using a single intervention: e.g. N-3 polyunsaturated fatty acids. In a recent study in coronary artery bypass grafting surgery patients, physical activity in the year before surgery showed a decrease in the incidence of postoperative atrial fibrillation during post-acute rehabilitation.[56]

Table 3 Single and multi-component interventions targeting single and multiple complications

		COMPLICATION	
		Single	***Multi***
INTERVENTION	***Single component***	**Effect found:** 1. N-3 polyunsaturated fatty acids (Calò et al., 2005[21], B-) targeting AF 2. 0.12% chlorhexidine gluconate (DeRiso et al., 1996[14], A2) targeting infections 3. Chlorhexidine mouth wash (Segers et al., 2008[15], A2) targeting infection 4. Nutritional supplement (Tepaske et al., 2001[16], A2) targeting infections 5. Glycine-enriched immune-enhancing supplement (Tepaske et al., 2007[17], A2) targeting infection and PPC 6. Respiratory physiotherapy (Yánez-Brage et al., 2009[49], B) targeting PPC 7. Ventilatory exercises (Garbossa et al., 2009[40], B) targeting anxiety **No effect found:** 1. Preadmission education (Watt-Watson et al., 2004[27], A2) targeting pain 2. Chaplain visits (Bay et al., 2008[38], B-) targeting depression 3. Omission of deep breathing exercises (Brasher et al., 2003[39], B) targeting early postoperative mobilization 4. No chest physiotherapy (Stiller et al., 1994[48], B) targeting PPC	**Effect found:** 1. Relaxation response training (Leserman et al., 1989[44], B-) targeting tension, anger, high BP and HR, low relaxation response, depression, fatigue, confusion and reduced vigor 2. Supervised exercise training (Arthur et al., 2000[37], B+) targeting prolonged ICU stay, prolonged LOS, decrease in QoL 3. Experimental videotapes (Mahler et al., 1998[45],B-) targeting PICULOS and prolonged LOS **No effect found:** 1. Preadmission education (Shuldham et al., 2002 [31], A2) targeting prolonged LOS, pain, anxiety, depression, and decreased general well-being 2. Oral rivastigmine (Gamberini et al., 2009[8], A2) targeting delirium ICU-stay and LOS 3. Intravenous hydration (Marathias, 2006[46], B) targeting MI, arrhythmia, duration of surgery, length of intubation, ICU stay, use of IABP, LOS, hospital death
	Multi component	**Effect found:** 1. Risk stratification and individualized inspiratory muscle training (Hulzebos et al., 2006[19], A2) targeting PPC	**Effect found:** 1. HeartOp programme (Furze et al., 2009[30], A2) targeting decrease in physical activity and depression 2. A nurse-led programme (Goodman et al., 2008[42], B+) targeting QoL, high BP, high cholesterol, high BMI, anxiety and depression 3. Health education and motivational interviews (McHugh et al., 2001[47], B-) targeting anxiety, depression, cigarette smoking, high BMI, high BP, decrease in physical activity and decrease in QoL 4. Preoperative relaxation skills training with music, massage and guided imagery (Kshettry et al., 2006[41], B-) targeting pain, anxiety and LOS 5. Individual instruction and a daily activities programme (Ku et al ., 2002[41], B-) targeting anxiety and LOS

PPC = postoperative pulmonary complications; BP = blood pressure; HR = heart rate; ICU = intensive care unit; LOS = length of hospital stay; QoL = quality of live; PICULOS = prolonged length of intensive care unit stay; IABP = intra-aortic balloon pump; BMI = body mass index;

To fully appreciate these results, three additional points must be considered. First, fourteen of the 23 studies were of fair quality (level B). The grading for this quality level has a range of methodological and statistical characteristics. A common shortcoming in the studies included in this systematic review was the reporting of the blinding of patients, caregivers and researchers (appendix 2). If patients or caregivers cannot be blinded, like in the case of chaplain visits as an intervention [38], still the researchers can be blinded. In many studies this was not reported. Another common shortcoming was the quality of the statistical analysis. In some of these studies, parametric statistical tests were used in a population that was not normally distributed. Therefore, we gave a grade of B- to studies with more shortcomings and a B+ to studies with fewer shortcomings (appendix 2).

Second, the more vulnerable older patients were not discussed separately in the identified articles. Therefore, although the majority of these populations is 65 years and older, we could not show which part of the identified evidence can be attributed to the older population and which part can be attributed to the younger and more vital population. This must be taken into account when our findings are generalized.

Third, we used a comprehensive search strategy so that we would not miss interventions. This comprehensive search strategy yielded divergent results, e.g. single and multi-component interventions targeting single and multiple complications. On one hand, due to multifactorial approach, one can argue that this review has a disparate nature. On the other hand, multifactorial geriatric syndromes in older patients require a multifactorial approach, which by nature will result in both tangible and less tangible results. Although the different outcomes were too divergent to be pooled as in a meta-analysis, the advantage of this multifactorial approach is that it provides an overview of the available preventive interventions.

Conclusion

In general, good quality studies found that multi-component interventions have an effect on preventing postoperative complications in older cardiac surgery patients. The current review indicates that there are several interventions that can decrease the occurrence of postoperative depression, pulmonary complications (both multi component interventions), atrial fibrillation (N-3 polyunsaturated fatty acids) and infection (combined disinfection and immune-enhancing nutritional supplements) in older cardiac surgery patients. To date there is no high quality evidence for measures aimed at preventing delirium and pressure ulcers in cardiac surgical patients in the preadmission period. Multifactorial approaches are the most promising, but solid research of effective preventive preadmission interventions for postoperative delirium and pressure ulcers is urgently needed.

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APPENDIX 1

PICO, Search Rule and Search Strategy

PICO:

Patient: Elderly Cardiac Surgery Patient **Intervention:** Treatment or Care
Comparison: Improve Quality of Live **Outcome:** Prevent a Postoperative Complication(s)

Query used for the literature search

(elderly OR aged OR aging OR geriatric OR long lived OR old OR older OR seni+ OR "middle aged") AND ("coronary Artery Bypass" OR "coronary Bypass" OR valve OR cardiac OR cardiovascular OR "cardiac procedure") AND (surgery OR surgical OR operation OR procedure OR incision) AND (intervention OR treatment OR nurse OR nursing OR care OR physiotherapy OR physiatrist OR physical therapy OR "physiologic intervention" OR "physiologic interventions" OR physiotherapeutic OR "occupational therapy" OR occupational OR nutrition OR aliment OR alimentation OR nourishment OR nutriment OR supplements OR "information provision" OR education OR advising OR instruction OR training OR schooling OR teaching OR guidance OR preparation OR tutoring OR coaching OR counselling OR exercised OR exercise OR exercised OR prehabilitation OR exercising OR exertion OR training OR workout) AND (("quality of life" OR "quality of living" OR "quality of wellbeing") OR ((preventive OR prevent OR impeding OR preventative) AND ("adverse events" OR "functional decline" OR "cognitive decline" OR "postoperative complication" OR "postoperative complications" OR "postoperative problems" OR "postoperative problem" OR "postoperative difficulties" OR "postoperative difficulty" OR "pressure ulcers" OR "pressure sores" OR bedsore OR "pressure necrosis" OR delirium OR "mental confusion" OR "postoperative mental confusion" OR "postoperative disorientation" OR depression OR gloom OR fall OR falls OR falling OR infection OR contamination)))

Table 1 Electronic search strategy March, 2011		Number of hits				
PICO	*Search queries*	*MEDLINE*	*EMBASE*	*Cochrane*	*Cinahl*	*PsychINFO*
Patient: Elderly cardiac surgery patient	1) (elderly OR aged OR aging OR geriatric OR long lived OR old OR older OR seni+ OR "middle aged")	2,510936	623,975	1,095	323,352	6,192
	2) ("coronary Artery Bypass" OR "coronary Bypass" OR valve OR cardiac OR cardiovascular OR "cardiac procedure")	60,424	146,970	252	6,325	3,861
	3) (surgery OR surgical OR operation OR procedure OR incision)	3,977,854	5,733,880	985	121,627	792
	1) AND 2) AND 3)	35,381	21,636	32	2,151	52
Inter-vention: Treatment or care	4) (intervention OR treatment OR nurse OR nursing OR care OR physiotherapy OR physiatrist OR physical therapy OR "physiologic intervention" OR "physiologic interventions" OR physiotherapeutic OR "occupational therapy" OR occupational OR nutrition OR aliment OR alimentation OR nourishment OR nutriment OR supplements OR "information provision" OR education OR advising OR instruction OR training OR schooling OR teaching OR guidance OR preparation OR tutoring OR coaching OR counselling OR exercised OR exercise OR exercised OR prehabilitation OR exercising OR exertion OR training OR workout)	5,442,873	2,955,682	3,586	833,361	487,946
Compa-rison: Improv. QoL	5) ("quality of life" OR "quality of living" OR "quality of wellbeing")	96,006	77,422	626	29,728	8,809

Table 1 Electronic search strategy March, 2011		**Number of hits**				
PICO	*Search queries*	*MEDLINE*	*EMBASE*	*Cochrane*	*Cinahl*	*PsychINFO*
Outcome: Prevent a post-operative compli-cation(s)	6) (preventive OR prevent OR impeding OR preventative)	220,817	165,478	1,016	29,815	98
	7) ("adverse events" OR "functional decline" OR "cognitive decline" OR "postoperative complication" OR "postoperative complications" OR "postoperative problems" OR "postoperative problem" OR "postoperative difficulties" OR "postoperative difficulty" OR "pressure ulcers" OR "pressure sores" OR bedsore OR "pressure necrosis" OR delirium OR "mental confusion" OR "postoperative mental confusion" OR "postoperative disorientation" OR depression OR gloom OR fall OR falls OR falling OR infection OR contamination)	1,132,120	1,513,991	1,522	109,237	10,158
	6) AND 7)	40,459	53,057	837	7,649	99
PICO	1) AND 2) AND 3) AND 4) AND (5) OR (6 AND 7))	924	262	25	70	3

APPENDIX 2 ***Methodological aspects of the included studies***

	RANDOMIZED CLINICAL TRIALS									
AUTHOR, YEAR	**RAN-DO-MIZED**	**ALLOCAT. CONCEAL-MENT**	**PAT. BLIND.**	**CARE-GIVER BLIND.**	**RESEAR-CHER BLIND.**	**INTERVENT. AND CONTROL GROUP COMPARISON**	**SUFF. FOLLOW -UP**	**INTEN-TION TO TREAT**	**APART FROM THE INTERV.: EQUAL TREATM. OF INTERV. AND CONTR. GROUP**	**STUDY QUAL. (RISK OF BIAS)***
Arthur, 2000	Yes	yes	no	yes	nr	yes	yes	yes	yes	**B+**
Bay, 2008	Yes	nr	nr	nr	yes	yes	no	yes	yes	**B-**
Brasher, 2003	Yes	nr	nr	nr	nr	yes	yes	yes	yes	**B**
Calò, 2005	Yes	yes	nr	nr	yes	yes	nr	yes	yes	**B-**
DeRiso, 1996	Yes	yes	yes	yes	nr	yes	yes	yes	yes	**A2**
Furze, 2009	Yes	yes	yes	nr	yes	yes	yes	yes	yes	**A2**
Gamberini, 2009	Yes	nr	yes	yes	yes	yes	yes	yes	yes	**A2**
Garbossa, 2009	Yes	yes	nr	yes	yes	yes	nr	nr	yes	**B**
Goodman, 2008	Yes	yes	nr	nr	nr	yes	yes	yes	yes	**B+**
Hulzebos, 2006	Yes	yes	no	yes	yes	yes	yes	yes	yes	**A2**
Kshettry, 2006	Yes	yes	nr	nr	nr	no/yes	yes	no	yes	**B-**
Ku, 2002	Yes	nr	yes	nr	nr	no/yes	nr	nr	yes	**B-**
Leserman, 1989	Yes	nr	nr	nr	nr	yes	no/yes	nr	yes	**B-**
Mahler, 1998	Yes	nr	nr	nr	yes	yes	yes	yes	yes	**B-**
Marathias, 2006	Yes	nr	no	no	no	yes	nr	yes	yes	**B**
McHugh, 2001	Yes	nr	nr	nr	nr	yes	no/yes	no	nr	**B-**
Segers, 2008	Yes	yes	yes	yes	yes	yes	yes	yes	yes	**A2**

APPENDIX 2 ***Methodological aspects of the included studies***

RANDOMIZED CLINICAL TRIALS										
AUTHOR, YEAR	RAN-DO-MIZED	ALLOCAT. CONCEAL-MENT	PAT. BLIND.	CARE-GIVER BLIND.	RESEAR-CHER BLIND.	INTERVENT. AND CONTROL GROUP COMPARISON	SUFF. FOLLOW -UP	INTEN-TION TO TREAT	APART FROM THE INTERV.: EQUAL TREATM. OF INTERV. AND CONTR. GROUP	STUDY QUAL. (RISK OF BIAS)*
Shuldham, 2002	Yes	yes	nr	yes	yes	no/yes	yes	yes	yes	**A2**
Stiller, 1994	Yes	nr	nr	yes	yes	yes	yes	nr	yes	**B**
Tepaske, 2001	Yes	yes	yes	yes	yes	no/yes	no/yes	no/yes	yes	**A2**
Tepaske, 2007	Yes	yes	yes	yes	nr	yes	yes	no	yes	**A2**
Watt-Watson, 2004	Yes	nr	yes	yes	yes	yes	yes	yes	yes	**A2**

COHORT STUDY											
AUTHOR, YEAR	DEFINED RE-SEARCH GROUPS	EXCLU-SION OF SELEC-TION BIAS	LEVEL OF EXPO-SURE DEFINED	ADEQUATE METHOD FOR ASSESSING THE EXPOSURE	OUT-COME DEFINED	ADEQUATE METHOD FOR ASSESSING THE OUTCOME	OUTCOME ASSESSMENT BLIND TO EXPOSURE STATUS	SUFFICIEN T TIME TO FOLLOW-UP	NO SELEC-TIVE FOLLOW -UP	MAIN PROGNOSTIC FACTORS OR CONFOUNDERS ACCOUNTED FOR	TOTAL RISK OF BIAS
Yánez-Brage, 2009	Yes	nr	yes	yes	yes	yes	no/yes	yes	yes	yes	**B**

nr = not reported; no/yes = it is presented, but not sufficient for a full yes

*) Study Quality: A2 means a good quality and B a fair quality; consequently the risk of bias in a study with quality B is larger than it is in a study with quality A2. Within the range of a fair quality B, we gave a grade of B- to studies with some more shortcomings and a B+ to studies with fewer shortcomings.

APPENDIX 3 Abstracted data from the 23 studies included in this systematic review

REF. DESIGN	COUNTRY, SETTING	TYPE OF SURGERY	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	CONTROL	N TOTAL (I-C)	AGE, MEAN (SD) I	AGE, MEAN (SD) C	FEMALE (%) I	FEMALE (%) C
Arthur, 2000 RCT	Canada, regional cardiovascular surgery centre	CABG	At least 10 weeks away from surgery date	Combined CABG/ valve surgery; LVEF less than 0.40; geographic or physical limitations	Individualized, prescribed exercise training twice per week in a supervised environment; education and reinforcement; and monthly nurse-initiated telephone calls to answer questions and provide reassurance	Usual care were followed by their primary care physicians, cardiologists, or surgeons	146 (123 – 123)	61.8 (8.4)	63.8 (7.8)	12.2	17.1
Bay, 2008 RCT	USA, 3 city hospitals	CABG	Speak and read English; have tele-phone access	Psychiatric illness	Five chaplain visits (average total visits time, 44 min), in the pre-surgery period during admission	Usual care, no chaplain visits	166 (83 – 83)	64 (na)	64 (na)	25	25
Bras-her, 2003 RCT	Australia, Medical Centre and Private hospital	Cardiac surgery	All cardiac surgery, including sternotom y	Unable to understand instructions in English; immobile due to prior neuro-logical or musculo-skeletal condition	No deep breathing exercises at each physiotherapy visit (leave this out of the usual care), in the pre-surgery period during admission	A set routine of deep breathing exercises at each physiotherapy visit (usual care)	230 (115 – 115)	63.3 (10.8	60.7 (10.9)	69	70

APPENDIX 3 Abstracted data from the 23 studies included in this systematic review

REF. DESIGN	COUNTRY, SETTING	TYPE OF SURGERY	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	CONTROL	N TOTAL (I-C)	AGE, MEAN (SD) I	AGE, MEAN (SD) C	FEMALE (%) I	FEMALE (%) C
Calò, 2005 RCT	Italy, Depart-ment of Cardiac Diseases city hospital	CABG	Normal sinus rhythm, and in stable hemodyna mic conditions before surgery	Need for concomitant valvular surgery; prior history of any kind of supraven-tricular arrhythmias; current use of antiarrhythmic medications other than beta-receptor antagonists, calcium-channel antagonists, or digitalis	N-3 polyunsaturated fatty acids (PUFAs) for a minimum of five days preoperative until discharge from the hospital, in preventing the occurrence of atrial fibrillation after CABG	Usual Care	160 (81 – 79)	64.9 (9.1)	66.2 (8.0)	16	14
DeRiso, 1996 RCT	USA, Tertiary care hospital	Cardiac surgery	Consecuti ve eligible patients who underwent CABG, valve surgery, septal surgery, cardiac tumor	Heart and lung transplantations. Intraoperative, death, preoperative infection or intubation, pregnancy, heart and lung transplant recipients, and known	0.12% chlorhexidine gluconate (CHX) oral rinse to prevent oropharyngeal deconta-mination on nosocomial infections in a comparatively homogeneous population of patients undergoing heart surgery, for 30 seconds twice daily	Placebo	353 (173 – 180)	64.1 (0.86	63.5 (0.84)	31	32

APPENDIX 3 Abstracted data from the 23 studies included in this systematic review

REF. DESIGN	COUNTRY, SETTING	TYPE OF SURGERY	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	CONTROL	N TOTAL (I-C)	AGE, MEAN (SD) I	AGE, MEAN (SD) C	FEMALE (%) I	FEMALE (%) C
			excision, or combined CABG valve surgery requiring CPB	hypersensitivity to CHX.	preoperative until ICU discharge						
Furze, 2009 RCT	UK, Hull and East Yorkshire Hospitals Trust	CABG	All patients admitted to the routine (non-urgent) waiting list for CABG at a cardiothoracic centre, ability to give informed consent	Exercise induced arrhythmias, loss of systolic BP greater than 20 mm Hg during exercise stress testing, unstable angina, a score of four on the Canadian Cardiovascular Society classification for angina or the NYHA classification of heart failure, current psychiatric problems, dementia, self-	Cognitive-behavioural intervention (the HeartOp Programme) to routine nurse counselling for people waiting for CABG surgery. 45–60 minute first interview (minimum of eight weeks before surgery) conducted in the outpatients clinic by the nurse facilitator, followed by ten to fifteen minute phone calls to their home at weeks one, three and six (± one week) and then monthly until they were admitted for their operation	Usual care	204 (100 – 104)	64.25 (8.81	65.29 (8.51)	85	76

APPENDIX 3 Abstracted data from the 23 studies included in this systematic review

REF. DESIGN	COUNTRY, SETTING	TYPE OF SURGERY	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	CONTROL	N TOTAL (I-C)	AGE, MEAN (SD) I	AGE, MEAN (SD) C	FEMALE (%) I	FEMALE (%) C
				report of periods of dizziness or confusion, life threatening comorbidities, concurrent particip. in other research.							
Gamberini, 2009 RCT	Switzerland, University Hospital Basel	Cardiac Surgery	Age 65 or older and elective cardiac surgery with cardiopulmonary bypass	Urgent/emergency; previous cardiac surgery, cardiac surgery combined with non-cardiac procedures; insuf-ficient knowledge of German or sensory impairment inter-fering with neuro-psychological testing; preoperative MMSE <15, psychiatric illness; antidepres-sants;	Prophylactic short-term administration of oral rivastigmine, a cholinesterase inhibitor: 1.5 mg of oral rivastigmine per day, from the evening before surgery until six days post-surgery	Placebo	120 (56 – 57)	74.1 (5.9)	74.4 (5.2)	30	34

APPENDIX 3 Abstracted data from the 23 studies included in this systematic review

REF. DESIGN	COUNTRY, SETTING	TYPE OF SURGERY	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	CONTROL	N TOTAL (I-C)	AGE, MEAN (SD) I	AGE, MEAN (SD) C	FEMALE (%) I	FEMALE (%) C
				antipsycho-tics; pre-existing neurologic deficits, previous or on-going treatment with cholinesterase inhibitors, and known contraindications for rivastigmine							
Garbos-sa, 2009 RCT	Brazil, Univer-sity Hospital	CABG	All scheduled CABG surgery	Informed consent	Physiotherapeutic instructions on anxiety; ventilatory exercise, from 24 hours before surgery until hospital admission	Usual care	51 (27 – 24)	64.5 (9.5)	62.6 (10.4)	25	33.3
Good-man, 2008 RCT	UK, Cardiac Home-care	CABG	At least one poorly controlled risk factor	Lived outside the designated geographical area; A life-threatening significant non-cardiovascular disease such as cancer.	Lifestyle counselling and preparation for surgery at monthly intervals (nurse-led programme of support and lifestyle management) , from a minimum of six weeks before surgery	Standard care, consisted of the hospital helpline telephone numbers and a pre-surgery infor-mation day in addition to a baseline assessment.	188 (94 – 94)	63.7 (na)	65.9 (na)	23.4	14

APPENDIX 3 Abstracted data from the 23 studies included in this systematic review

REF. DESIGN	COUNTRY, SETTING	TYPE OF SURGERY	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	CONTROL	N TOTAL (I-C)	AGE, MEAN (SD) I	AGE, MEAN (SD) C	FEMALE (%) I	FEMALE (%) C
Hulzebos, 2006 RCT	Netherlands, University Hospital	CABG	Scheduled for primary elective CABG surgery; informed consent; at high risk of developing PPCs based on Preoperative Risk Stratification.	Surgery performed within two weeks of initial contact, a history of cerebrovascular accident, use of immune suppressive medication for 30 days before surgery, and presence of a neuromuscular disorder, cardiovascular instability, or an aneurysm	Preoperative Assessment and Risk Stratification + individualized, tailored inspiratory muscle training (IMT) seven times a week, for at least two weeks before surgery, twenty minutes, six times a week without supervision and once with supervision by a phys. therapist, who measured the strength and endurance of the inspi-ratory muscles after each week of training	Care as usual the day before surgery (ie, instruct. on deep breathing manoeuvres, coughing, and early mobilization)	279 (140 – 139)	66.5 (9.0)	67.3 (9.2)	22.3	21.9
Kshettry, 2006 RCT	USA, regional hospital	Cardiac Surgery	Elective or emergent heart surgery; available for follow-up 6 to 8 weeks after surgery	Active psychosis; not read and write English	Preoperative relaxation skills training with guided imagery and a 30-minute gentle touch or light massage using the comple-mentary alternative medical therapies package (eg, music, massage, and guided imagery) and postoperative treatment by a team of healing coaches, all during hospitalization	Usual care	104 (53 – 51)	62.8 (13.4)	63.5 (14.12)	37.7	17.6

APPENDIX 3 Abstracted data from the 23 studies included in this systematic review

REF. DESIGN	COUNTRY, SETTING	TYPE OF SURGERY	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	CONTROL	N TOTAL (I-C)	AGE, MEAN (SD) I	AGE, MEAN (SD) C	FEMALE (%) I	FEMALE (%) C
Ku, 2002 RCT	Taiwan, Veterans General Hospital	CABG	Under-stand and speak Mandarin and/or Taiwa-nese; read Chinese or with interpreter ; no prev. cardiac surgery; no known neurologic problem	na	Individual instruction in progressive exercises and daily activities according to the phase I cardiac rehabi-litation programme (Chinese manual) were used during hospitalization (Chinese manual illustrating indications and contra-indications of cardiac rehabili-tation, general prin-ciples of exercise prescription, and exercise programs (ie, passive to active range of motion of major muscle groups, active ankle exercises, active scapular lift, deep breathing, monitored oximetry walking, and stair-climbing), and a daily activities programme (i.e., sitting in chair, walking, and participating in activities of daily living and personal care as needed) during hospitalization	Usual care	60 (30 – 30)	68.47 (7.20)	69.03 (8.12)	13.3	20
Leser-man, 1989 RCT	USA, city hospital	Cardiac Surgery	Valve and coronary surgery procedures	na	Twice a day training in eliciting the relaxation response before and after surgery, started two to seven days before surgery	Usual care	27 (13 – 14)	65.3 (7.1)	69.6 (9.7)	52	36

APPENDIX 3 Abstracted data from the 23 studies included in this systematic review

REF. DESIGN	COUNTRY, SETTING	TYPE OF SURGERY	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	CONTROL	N TOTAL (I-C)	AGE, MEAN (SD) I	AGE, MEAN (SD) C	FEMALE (%) I	FEMALE (%) C
Mahler, 1998 RCT	USA, 2 city hospitals	CABG	na	na	Three experimental videotapes that involved different approaches for preparing CABG patients for surgery and the in hospital recovery period. One of the tapes conveyed information via a health care expert only. The other two featured the same health care expert and also inclu-ded clips of interviews with patient models. These latter two tapes differed in the extent to which they portrayed the recovery period as a steady, forward pro-gresssion or as consisting of "'ups and downs", on the evening prior to surgery	Usual care	257 (60/65/65 – 67)	na* (na)	na* (na)	0	0
Mara-thias, 2006 RCT	Greece, tertiary cardiac surgery center	Cardiac Surgery with Chronic Kidney Disease	Admitted for elective open heart surgery at Onassis Cardiac Surgery Center, who suffered from moderate to severe CKD (glomerular filtration rate calculated by	na	Intravenous hydration for twelve hours prior to cardiac surgery	Fluid restriction	45 (30 – 15)	64 (1.7)	64.2 (2.8)	3	7

APPENDIX 3 Abstracted data from the 23 studies included in this systematic review

REF. DESIGN	COUNTRY, SETTING	TYPE OF SURGERY	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	CONTROL	N TOTAL (I-C)	AGE, MEAN (SD) I	AGE, MEAN (SD) C	FEMALE (%) I	FEMALE (%) C
			the Cockroft-Gault equation less than 45 mL/min)								
Mc-Hugh, 2001 RCT	Scotland UK, Community and a university hospital	CABG	na	na	Health education and motivational interviews, according to individual need, was carried out monthly. Care was provided in the patients' own homes by the commu-nity based cardiac liaison nurse alterna-ting with the general practice nurse at the practice clinic, in a mean waiting time of eight and half months	Usual care	122 (62 – 59)	Median (IQR) 61.1 (35-77)	Median (IQR) 63 (42-76)	28.6	20.4
Segers, 2008 RCT	Netherlands, city hospital	Cardiac Surgery	18 years or older	Emergent/urgent; preoperative infection/-antibiotic use; allergic for chlorhexidine; other profilactic treatment	Chlorhexidine mouth wash (10 ml) 4x daily 30 seconds, and nasal gel 4x daily in both nostrils, from admission to one day post-surgery	Placebo	991 (500 – 491)	65.3 (10.4)	66.4 (9.9)	25.4	28.4

APPENDIX 3 Abstracted data from the 23 studies included in this systematic review

REF. DESIGN	COUNTRY, SETTING	TYPE OF SURGERY	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	CONTROL	N TOTAL (I-C)	AGE, MEAN (SD) I	AGE, MEAN (SD) C	FEMALE (%) I	FEMALE (%) C
Shuld-ham, 2002 RCT	UK, City hospital	CABG	≥18 years; having a first episode of CABG surgery; willing and able to attend edu-cation clinics	na	Approximately four hours of education early in the waiting period prior to admission, by members of the multidisciplinary team	Usual care	356 (188 – 168)	62.7 (7.46)	62.3 (8.46)	10	15
Stiller, 1994 RCT	Australia, City hospital	CABG	Elective surgery	Unable to understand written or spoken English	*Intervention 1)* No chest physiotherapy preoperative or postoperative during admission *Intervention 2)* Preoperatively four times a day physiotherapy on the first two postoperative days and twice daily on the third and fourth postoperative days, including the usual chest physiotherapy	Treatment for this group consisted of the usual chest Physiotherapy	120 (40-40-40)	62 (11)/ 61 (9)	63 (8)	18/18	25
Tepas-ke, 2001 RCT	Nether-lands, City hospital	Cardiac Surgery	One or more of the following	Younger than twenty-one years; pregnant, insulin-dependent	Preoperative oral immune-enhancing nutritional supplement for a	Placebo	45 (23 – 22)	66.8 (11.6)	70.2 (6.9)	35	41

APPENDIX 3 Abstracted data from the 23 studies included in this systematic review

REF. DESIGN	COUNTRY, SETTING	TYPE OF SURGERY	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	CONTROL	N TOTAL (I-C)	AGE, MEAN (SD) I	AGE, MEAN (SD) C	FEMALE (%) I	FEMALE (%) C
			criteria: Age 70 years or older, ejection fraction less than 0·40, or replacement of mitral valve	diabetes mellitus; severe renal or liver failure; malignancy, used immune sup-pressive medication or used non-steroidal anti-inflammatory drugs (except aspirin) on a long-term basis	minimum of five days for a minimum five to ten days before the operation during admission						
Tepas-ke, 2007 RCT	Nether-lands, City hospital	High-Risk Cardiac Surgery	One or more of the following criteria: Age 70 years or older, LVEF less than 0.40, or planned mitral valve surgery	<21 years; pregnant; insulin-dependent diabetes mellitus; severe renal or liver failure; malignancy; used immune sup-presssive medication or non-steroidal anti-inflammatory drugs (except acetylsalicylic acid)	*Intervention 1)* Glycine-enriched immune enhancing formula, Oral Impact glycine enriched; or *Intervention 2)* Standard preoperative immune-enhancing-formula; Both interventions five to ten days preoperative, during admission	Control formula	70 (22-24-24)	Mean 95CI 1) 73.2 (70.9 – 75.3) 2) 71.8 (68.3 – 74.8)	Mean 95CI 71.5 (68.3-74.2)	1) 45 2) 33	63

APPENDIX 3 Abstracted data from the 23 studies included in this systematic review

REF. DESIGN	COUNTRY, SETTING	TYPE OF SURGERY	INCLUSION CRITERIA	EXCLUSION CRITERIA	INTERVENTION	CONTROL	N TOTAL (I-C)	AGE, MEAN (SD) I	AGE, MEAN (SD) C	FEMALE (%) I	FEMALE (%) C
Watt-Watson, 2004 RCT	Canada, City hospital	CABG	Elective; first uncompl. CABG surgery; attending preadmission educ. session; able to under-stand, read, and speak English	Repeated CABG and/or valve surgery	Preadmission education two to seven days prior surgery, standard care + pain booklet group booklet focused on communicating pain and the use of analgesics during admission	Usual care	406 (204 – 202)	61.7 (9.3)	61.9 (9.4)	13	17
Yánez-Brage, 2009 Cohort	Spain, Univer-sity Hospital	Off-pump CABG	Consecutive patients aged 18 and over	Emergency; on-pump CABG surgery; severe endocarditis; history of stroke, re-intervention; and psychological disorders	Respiratory physiotherapy the morning after admittance pre-surgery and the morning after surgery	Usual care	263 (159 – 104)	65.9 (9.6)	67.1 (9.1)	17.0	22.1

na = not available (not reported), CABG = Coronary Artery Bypass Grafting surgery procedure, LVEF = Left Ventricular Ejection Fraction, CHX = Chlorhexidine gluconate, BP = Blood Pressure, MMSE = Minimal Mental State Examination, PPCs = Postoperative Pulmonary Complications,
* Figures provided per hospital, not for the intervention group and control group respectively

APPENDIX 4 ***Abstracted outcome data for the 22 randomized clinical trials and 1 cohort study included in this systematic review***

STUDIES	OUTCOME MEASURE	INTERVENTION	CONTROL	P-VALUE	EFFECT SIZE*
Arthur, 2000	Time until order for discharge from ICU, h median (IQR)	19.67 (15.91–23.25)	21.16 (18.49–39.57)	0.001	-0.1414†
	ICU length of stay, hour median (IQR)	24.67 (21.68–41.85)	26.71 (22.76–46.50)	0.038	-0.1719†
	Time spent in the hospital after surgery, d median (IQR)	5 (5–6)	6 (5–7)	0.001	-1†
	LOS, d median (IQR)	6 (5–7)	7 (6–8)	0.002	-0.5†
	SF-36 Physical role	9.46 ± 34.39	-2.06 ± 33.70	0.01	-0.3418
	SF-36 Physical function	-1.17 ± 18.46	-6.56 ± 20.12	0.04	-0.2679
	SF-36 General health	8.22 ± 18.20	4.14 ± 18.78	0.10	-0.2173
	SF-36 Bodily pain	3.58 ± 22.24	4.11 ± 20.54	<0.2	0.0258
	Physical Composite Summary Score	*1.55 ± 7.48*	*-1.46 ± 7.81*	*0.04*	*-0.3854*
	SF-36 Vitality	-0.95 ± 18.46	-1.19 ± 15.48	<0.2	-0.155
	SF-36 Social functioning	4.50 ± 24.70	0.92 ± 24.10	<0.2	-0.1485
	SF-36 Emotional role	7.51 ± 45.32	16.82 ± 44.82	0.13	0.2077
	SF-36 Mental health	2.05 ± 18.52	0.77 ± 17.11	<0.2	-0.0748
	Mental Composite Summary Score	*1.54 ± 10.55*	*2.93 ± 9.15*	*<0.2*	*0.1519*
Bay, 2008	Anxiety (HADS) .	nr	nr	0.623	-
	Depression (HADS)	nr	nr	0.421	-
	Hope (Hearth Hope Index)	nr	nr	0.987	-
	Positive Religious Coping (RCOPE)	nr	nr	0.081	-
	Negative Religious Coping (RCOPE)	nr	nr	0.056	-
	Collaborative Religious Coping (RPSS)	nr	nr	0.218	-
	SelfDirecting Religious Coping (RPSS)	nr	nr	0.519	-
	Deferring Religious Coping (RPSS)	nr	nr	0.597	-
Brasher, 2003	length of stay	8.28 ±8.76	8.04 (±6.36	0.69	0.0377
	post-operative pulmonary complications	3 (2.6%)	5 (4.3%)	0.72	-
	FEV	50.0% ±13.1%	50.6% ±23.7%	0.84	-0.0253
	FVC	51.4% ±12.84%	52.1% ±21.5%	0.80	-0.0326
Calò, 2005	Atrial Fibrilation	15.2%	33.3%	0.013	-
	LOS	7.3 ± 2.1	8.2 ± 2.6	0.017	-0.3462
DeRiso	Number of infected patients	8	24	<0.01	-

APPENDIX 4 ***Abstracted outcome data for the 22 randomized clinical trials and 1 cohort study included in this systematic review***

STUDIES	OUTCOME MEASURE	INTERVENTION	CONTROL	P-VALUE	EFFECT SIZE*
(1996)	Total number of infections (mean±SD)	11 (0.06 ±0.002)	29 (0.16 ±0.002)	<0.05	-45.4545
	No. of patients with Systemic antibiotics	23	42	<0.05	-
Furze, 2009	Cardiac depression scale	81.69	93.37	0.008	-
	Clasp mobility	8.10	9.05	0.001	-
	Cardiac beliefs	4.10	7.61	<0.001	-
	0 visits to NHS GP (%)	75 (75.0)	82 (78.9)	nr	-
	1–2 visits to NHS GP (%)	21 (21.0)	19 (18.3)	nr	-
	≥3 visits to NHS GP (%)	4 (4.0)	3 (2.9)	nr	-
	Mean cost (£)	24.10 ±6.9	22.37 ±6.7)	nr	0.2507
	QALY	0.109±0.003	0.103 ±0.003	nr	2
Gambe-rini (2009)	Incidence of delirium, n (%)	17 (30)	18 (32)	0.8	-
	MMSE BL: day 2, median (range)	1(4–16)	1 (3–16)	1.0	0†
	CDT: day 2, median (range)	0 (3–6)	0 (1–6)	0.9	0†
	MMSE minimal value, median (range)	24 (10–29)	25 (12–30)	1.0	0.1111†
	CDT minimal value, median (range)	5 (0–6)	5 (0–6)	1.0	0†
	Duration of delirium, days: median (range)	3 (1–6)	2.5 (1–5)	0.3	0.25†
	Haloperidol rescue medication, n (%)	18 (32)	17 (30)	0.9	-
	Haloperidol mg/patient, median (range)	4.75 (1–53)	4 (1–25)	0.5	0.0625†
	Lorazepam rescue medication, n (%)	38 (68)	35 (61)	0.6	-
	Lorazepam mg/patient, median (range)	2 (1–21)	2 (1–6)	0.7	0†
	Days in ICU, median (range)	2 (2–6)	2 (2–7)	0.9	0†
	Days in hospital, median (range)	13 (7–39)	13 (7–39)	0.3	0†
Garbos-sa, 2009	Anxiety (preoperative physiotherapy)	9.6 ± 7.2	13.4 ± 5.9	0.02	-0.6678
	Anxiety (postoperative physiotherapy)	7.1 ± 5.2	8.7 ± 8.0	0.64	-0.2
Good-man (2008)	Systolic blood pressure (mm Hg) Change in mean and SD	−13.02 ± 20.35	−9.11 ± 20.49	0.12	-0.1908
	Diastolic blood pressure (mm Hg)	−7.97 ± 11.37	−5.38 ± 12.61	0.15	-0.2054
	Total cholesterol (mmol/l)	−0.18 ± 0.74	−0.20 ± 0.76	0.87	0.0263
	HDL cholesterol (mmol/l)	−0.02 ± 0.17	−0.01 ± 0.17	0.60	-0.0588
	Body Mass Index (kg/m2)	−0.16 ± 1.48	−0.08 ± 1.27	0.70	0.063
	HAD score-depression	−0.39 ± 2.73	0.18 ± 2.45	0.45	-0.2327
	HAD score-anxiety	−0.19 ± 2.81	0.14 ± 3.3	0.69	-0.1
	LOS in days, median (IQR), [range]	9 (3), [4–50]	8.5 (3.25), [2–170]	0.29	-0.3077

APPENDIX 4 ***Abstracted outcome data for the 22 randomized clinical trials and 1 cohort study included in this systematic review***

STUDIES	OUTCOME MEASURE	INTERVENTION	CONTROL	P-VALUE	EFFECT SIZE*
	SF36 Mental component summary scale	3.33 ± 13.13	2.57 ± 10.75	0.70	0.0707
	SF36 Physical component summary scale	−0.41 ± 7.50	−3.33 ± 7.58	0.04	0.3852
	CROQ physical health scale	−0.09 ± 12.72	−0.18 ± 18.53	0.91	0.0049
	CROQ cognitive health scale	0.80 ± 16.80	−0.09 ± 21.66	0.53	0.0411
	CROQ psychosocial health scale	2.24 ± 14.14	−1.81 ± 17.92	0.22	0.226
	CROQ symptom scale	−0.91 ± 13.56	−0.64 ± 13.68	0.37	0.0197
Hulze-bos (2006)	Duration of postoperative hospitalization, median (range), d	7 (5.41)	8 (6.70)	0.02	-
	PPC Grade 1	114 (82.0)	89 (65.0)	0.02	-
	PPC Grade 2	14 (82.0)	18 (65.0)	0.02	-
	PPC Grade 3	10 (7.2)	24 (17.5)	0.01	-
	PPC Grade 4	1 (0.7)	6 (4.4)	0.09	-
	PPC grade ≥2	25 (18.0)	48 (35.0)	0.02	-
	Pneumonia	9 (6.5)	22 (16.1)	0.01	-
Kshettry, 2006	Heart rate day1	81±14	84 ±16	NS	-0.19
	day2	77 ±13	82 ±13	NS	-0.38
	Systolic BP day1	120 ±18	114 ±18	NS	-0.33
	day2	114 ±14	112 ±17	NS	0.12
	Diastolic BP day1	60 ±10	61 ±12/	NS	-0.08
	day2	60 ±10	60 ±9	NS	0
	Pain and tension day1	2.4 ±1.9	3.5 ±2.6	<0.001	-0.42
	day2	1.3 ±1.3	2.1 ±2	<0.001	-0.65
Ku, 2002	Anxiety	28.6 ± 7	38.4 ± 9.1	<0 .001	-1.0769
	LOS	10.6 days	12 days	0.228	-
Leser-man, 1989	Systolic BP (mean change before and after)	-1.5	-3.4	0.3	-
	Diastolic BP	-3.8	-4.3	0.43	-
	Heart rate	17.7	15.4	0.26	-
	Relaxation response	0.44	1.17	0.4	-
	Tension	-18.5	-5.5	0.04	-
	Depression	-6.0	-2.0	0.2	-
	Anger	-4.6	4.1	0.04	-
	Fatigue	-0.2	2.2	0.28	-

APPENDIX 4 ***Abstracted outcome data for the 22 randomized clinical trials and 1 cohort study included in this systematic review***

STUDIES	OUTCOME MEASURE	INTERVENTION	CONTROL	P-VALUE	EFFECT SIZE*
	Vigor	-2.0	-2.1	0.5	-
	Confusion	-2.1	1.2	0.15	-
Mahler	Sample 1 (Scripps Mem. Hospital): ICU Days , mean (SD)		1.50 (0.16)	<.05	
(1998)	Coping tape	1.41 ±0.17		<.05	-0.5625
	Mastery tape	1.27 ± (0.12		<.05	-1.4375
	Nurse tape	1.44 ± (0.22		<.05	-0.375
	Sample 1 (Scripps Mem. Hospital): Postop LOS in Days		5.47 (0.22)	<.05	
	Coping tape	5.40 ±0.27		<.05	-0.3182
	Mastery tape	5.05 ±0.19		<.05	-1.9091
	Nurse tape	5.37 ±0.27		<.05	-0.4545
	Sample 2 (San Diego Veter. Affairs Med. Centre): ICU Days,		4.29 (1.19)	<.05	
	Coping tape	2.26 ±0.15		<.05	-1.7059
	Mastery tape	2.81 ±0.27		<.05	-1.2437
	Nurse tape	2.95 ±0.48		<.05	-1.1261
	Sample 2 (San Diego Veter.Affairs Med.Centre): Postop. Days		10.61 (1.56)	<.05	
	Coping tape	7.63 ±0.41		<.05	-1.9103
	Mastery tape	7.87 ±0.49		<.05	-1.7564
	Nurse tape	9.01 ±1.03		<.05	-1.0256
Mara-	Perioperative MI, n (%)	1 (3)	2 (13)	0.5	-
thias	Postoperative arrhythmia, n (%)	10 (33)	9 (60)	0.1	-
(2006)	CPB time (min)	89.7 ±10.7	95.9 ±14.5	0.7	-0.4276
	Aortic cross-clamp time (min)	70.9 ±6	73.3 ±10.4	0.8	-0.2308
	Duration of surgery (min)	273 ±13	257 ±16	0.5	1
	Length of intubation (h)	18 ±4	33 ±11	0.1	-1.3636
	ICU length of stay (h)	72 ±17	112 ±31	0.2	-1.2903
	Use of IABP, n (%)	2 (6)	0 (0)	0.5	-
	Hospital stay (days)	8.8 ±0.6	11.2 ±1.7	0.1	-1.4118
	In-hospital mortality (n)	0	0	1	-
Mc-	Cigarette smokers (%)	2	18	0.001	-
Hugh	Body mass index (kg/m^2)	27.1±3.1	28.1 ±3.4	0.000	-0.2941
(2001)	Seven day recall activity (min)	311.0 ±453.1	158.9 ±246.7	0.000	0.6165
	Plasma cholesterol (mmol/l)	5.1±0.7	5.6 ±1.0	0.003	-0.5

APPENDIX 4 ***Abstracted outcome data for the 22 randomized clinical trials and 1 cohort study included in this systematic review***

STUDIES	OUTCOME MEASURE	INTERVENTION	CONTROL	P-VALUE	EFFECT SIZE*
	Systolic BP (mmHg)	126.2 ±13.5	138.9 ±16.5	0.000	-0.7697
	Diastolic BP (mmHg)	69.2 ±8.5	82.3 ±10.8	0.048	-1.213
	SF-36 Physical function	38.0 ±27	24.3 ±25	0.005	0.548
	SF-36 Physical role limitation	22.2 ±37	11.2 ±28	0.003	0.3929
	SF-36 Emotional role limitation	61.9 ±46	22.4 ±36 32.3 ±27	0.000	1.0972
	SF-36 Social functioning	54.2 ±30	47.5 ±23	0.000	0.8111
	SF-36 Mental health	68.7 ±20	21.5 ±21	0.000	0.9217
	SF-36 Energy and vitality	36.5 ±21	38.0 ±25	0.000	0.7143
	SF-36 Pain	54.0 ±26	33.1 ±22	0.000	0.64
	SF-36 General health perception	43.7 ±20		0.000	0.4818
Segers (2008)	Total number of nosocomial infections	116	164	0.002	-
	Total number of postoperative woundinfections	48	52	0.61	-
	LOS mean days	8.3	15.2	<0.001	-
Shuld-ham (2002)	Anxiety Median change (range)	2 (-9 to 13)	2 (-8 to 13)	0.09	0†
	Pain Median change (range)	11 (-86 to 98)	11 (-83 to 82)	0.48	0†
	Depression Median change (range)	2 (-7 to 14)	2 (-8 to 12)	0.62	0†
	General Well-Being Worn out Median change (range)	2 (-19 to 20)	3 (-14 to 30)	0.11	-0.0455†
	General Well-Being Tense and uptight Median change (range)	3 (-13 to 21)	3 (-13 to 34)	0.29	0†
	Length of stay Mean (SD)	10.07 ±5.04	9.15 ±4,38	0.01	0.21†
Stiller, 1994	Number of Additional antibiotics Group preop. education (1)	8	8	NS	-
	Group preop education + intensive physiotharapy postop. (2)	15		NS	-
	Number of Bronchodilators Group preop. education	16	13	NS	-
	Group preop education + intensive physiotharapy postop.	18		NS	-
	Number of Inotropic, diuretic, antiarrhythmic drugs Group 1	11	16	NS	-
	Group 2	19		NS	-
	Length of postoperative stay Group 1	9.0 ± 5.7	8.5 ± 2.6	NS	0.1923
	Group 2	10.4 ± 6.9		NS	0.8077
	Number of patients with PPC Group 1	2	3	NS	-
	Group 2	4		NS	-
Tepas-ke, 2001	One or more infections	4	12	0.013	-
	Pneumonia	3	9	0.047	-
	Urinary tract infection	2	1	1.000	-

APPENDIX 4 ***Abstracted outcome data for the 22 randomized clinical trials and 1 cohort study included in this systematic review***

STUDIES	OUTCOME MEASURE	INTERVENTION	CONTROL	P-VALUE	EFFECT SIZE*
	Wound infection	0	2	0.233	-
	Temperature >38°C	1.28	1.27	0.808	-
Tepas-	Postoperative nutrition: Nasogastric tube feeding (no. patients)		3 ±0.87	0.203	
ke, 2007	oral immune-enhancing supplement with additional glycine (1)	6 ±0.87			3.4483
	oral immune-enhancing supplement (2)	8 ±2.5			5.7471
	Postoperative nutrition: Nasogastric tube feeding (mean cum,		1070 ±124.45	0.819	
	mL)	472 ±236.04			-4.8051
	(1)(2)	875 ±247.24	12		-1.5669
	Number patients with 1 or more infection(s)			0.02	
	(1)	5			-
	(2)	4	10		-
	Pneumonia			0.9	
	(1)	4			-
	(2)	4	4		-
	Urinary tract infection			0.12	
	(1)	2			-
	(2)	0	0		-
	Wound infection			0.71	
	(1)	1			-
	(2)	0	4.02 ±0.2		-
	Temperature >38°C			0.15	
	(1)	2.88 ±0.24			-5.7
	(2)	2.95 ±0.14	3.22 ±0.33		-5.35
	Number of days antibiotics			0.49	
	(1)	2.35 ±0.28			-2.63
	(2)	2.27 ±0.22			-2.8788

APPENDIX 4 ***Abstracted outcome data for the 22 randomized clinical trials and 1 cohort study included in this systematic review***

STUDIES	OUTCOME MEASURE	INTERVENTION	CONTROL	P-VALUE	EFFECT SIZE*
Watt-Watson (2004)	Analgesic administration (morphine equivalents mg/24 h) Day 1	21 ± 11	21 ± 12	NS	0
		29 ± 15	30 ± 14	NS	-0.0714
	Day 2	27 ± 16	28 ± 17	NS	-0.0588
	Day 3	22 ± 15	22 ± 17	NS	0
	Day 4	20 ± 16	20 ± 17	NS	0
	Day 5	152 ± 59	151 ± 59	NS	0.0169
	Analgesic prescription (morphine equivalents mg/24 h) Day 1	85 ± 35	85 ± 34	NS	0
	Day 2	62 ± 27	68 ± 43	NS	-0.1395
	Day 3	57 ± 16	60 ± 24	NS	-0.125
	Day 4	56 ± 14	58 ± 21	NS	-0.0952
	Day 5				
Yánez-Brage, 2009	Atelectasis	17.3%	36.3%	0.01	-
	Pleural effusion	48.1%	47.1%	0.87	-
	Pneumothorax	2.6%	2.0%	0.75	-
	Pneumonia	2.6%	1.0%	0.36	-
	Pulmonary Oedema	10.3%	4.9%	0.12	-
	Diaphragm elevation	89.7%	92.2%	0.51	-
	Renal insufficiency	1.3%	1.0%	0.82	-
	Neurological	0.6%	1.0%	0.77	-
	Wound infection	1.9%	1.0%	0.54	-
	Sternal instability	3.2%	0.0%	0.16	-
	Sternal dehiscence	3.8%	0.0%	0.08	-
	Scar dehiscence	1.9%	0.0%	0.28	-
	Death	1.3%	1.0%	0.82	-

*) The effect size was calculated by the difference between the means of the intervention and control group divided by the standard deviation of the control group.
†) When median with the interquartile range was reported the effect size was approximated by calculating the difference between the medians of the intervention and control group divided by the half of the interquartile range of the control group.
nr = not reported, NS = not significant (p-value ≥ 0.05), IQR = Inter Quartile Range, SE = Standard Error, SD = Standard Deviation, ICU = Intensive Care Unit, LOS = Length Of hospital Stay, SF-36 = Short Form 36 item quality of live score, HADS/ HAD score = Hospital Anxiety and Depression Score, RCOPE = 14 item positive or negative Religious Coping score, RPSS = Collaborative, Self-Directing, Deferring Religious Coping Score, FEV = forced expiratory volume in one second, FVC = forced vital capacity, NHS GP = National Health Service General Practitioner, QALY = Quality-Adjusted Life Year, MMSE = Minimal Mental State Examination, CDT BL = clock drawing test, CROQ = Coronary Revascularisation Outcome Questionnaire (cardiac specific quality of life measurement tool), PPC = Post Pulmonary Complication, BP = Blood Pressure, CPB time = cardiopulmonary bypass duration, IABP = Intra-Aortic Balloon Pump

Chapter 5

Development of a nursing intervention to prepare frail older patients for cardiac surgery (the PREDOCS Programme), following phase one of the guidelines of the Medical Research Council

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ABSTRACT

Background: In older patients undergoing elective cardiac surgery, the timely identification and preparation of patients at risk for frequent postoperative hospital complications provide opportunities to reduce the risk of these complications.

Aims: We developed an evidence-based multi-component nursing intervention (Prevention of Decline in Older Cardiac Surgery Patients; the PREDOCS Programme) for application in the preadmission period to improve patients' physical and psychosocial condition to reduce their risk of postoperative complications. This paper describes in detail the process used to design and develop this multi-component intervention.

Methods: In a team of researchers, experts, cardiac surgeons, registered cardiac surgery nurses, and patients, the revised guidelines for developing and evaluating complex interventions of the New Medical Research Council (MRC) were followed, including identifying existing evidence, identifying and developing theory, and modelling the process and outcomes. Additionally, the criteria for reporting the development of complex interventions in healthcare (CReDECI) were followed.

Results: The intervention is administered during a consult by the nurse two to four weeks before the surgery procedure. The consult includes three parts: a general part for all patients, a second part in which patients with an increased risk are identified, and a third part in which selected patients are informed about how to prepare themselves for the hospital admission to reduce their risk.

Conclusions: Following the MRC guidelines, an extended stepwise multi-method procedure was used to develop the multi-component nursing intervention to prepare older patients for cardiac surgery, creating transparency in the assumed working mechanisms. Additionally, a detailed description of the intervention is provided.

KEYWORDS

Frailty; Older People; Cardiac Surgery; Prevention; Postoperative Complications

INTRODUCTION

Increasingly older, sicker, and higher-risk patients undergo cardiac surgery. This is not only a consequence of the rapidly growing group of older people in the western world but also a result of improvements in surgical techniques and anaesthetic procedures that now allow surgery even in frail patients.[1-4]

Older patients, here defined as those ≥65 years of age, account for almost 60% of cardiac surgery patients and have variable post-surgical outcomes.[2-6] Frequent postoperative events in these patients include delirium (17 to 43%)[7,8], depression (18 to 28%)[9,10], pressure ulcer (14 to 18%)[11,12], and nosocomial infection (11 to 55%).[13-16] These complications are associated with functional and cognitive decline and a decrease in quality of life after discharge.[17]

Different mechanisms underlie the development of each of these four highly prevalent complications. Multi-component approaches are more powerful than single-component approaches because they can address a greater number of potential risk factors (paradigm of multi-causality).[18,19] Because the geriatric population is highly heterogeneous with respect to frailty, risk identification approaches should be included in the workup process.[20,21] It is widely accepted that vulnerable patients should be identified and optimally prepared before a cardiac surgery procedure.[22-24] As more than 95% of cardiac surgeries are conducted electively, most patients have a waiting period before admission to the hospital, which allows for the more timely identification of patients at high risk for postoperative complications and preparation to reduce their risk.[22,23,25] This creates a window of opportunity to initiate prevention before the hospital admission.

While preparing older patients for cardiac surgery in the preadmission period and focusing on a comprehensive approach aimed at reducing the incidence all four complications, a multi-component intervention is desirable. Such interventions when provided by a skilled nurse have been shown to be effective in reducing complication risk.[19-21] Multi-component or complex interventions are defined as interventions that include several interacting (multi) components and variable outcomes.[26-28] In the literature, adequate details and precise descriptions of multi-component interventions and their development process are often lacking.[28,29] Insufficient reporting hinders in-depth review and replication of the proposed interventions. Consequently, insufficient reporting also makes it difficult to validate complex interventions. Therefore, the British New Medical Research Council (MRC) proposed guidelines for developing multi-component or complex interventions that describe appropriate methods to use.[27,28,30-32] Recently, criteria for reporting the development and evaluation of complex interventions in healthcare (CReDECI-criteria) were proposed.[29]

The purpose of this research Programme was to develop a multi-component nursing intervention for application in the preadmission period with the goal of improving the patient's physical and psychosocial condition to reduce the risk of postoperative complications in high-risk, frail, older cardiac surgery patients. To understand the different

components, this paper describes in detail the process used to design and develop this multi-component intervention, and we provide a detailed description of the proposed intervention.

METHODS

Based on the linear sequenced phases of drug development that are used in the design, evaluation, and implementation of complex interventions, in 2000, the MRC developed a framework. In 2008, a revised version was published in which the process of developing and evaluating complex interventions was described according to cyclical phases. Both models showing the evolution of the Medical Research Council guidelines are presented in appendix 1.

We followed the revised MRC guidelines concerning the procedure for developing a multi-component or complex intervention. This procedure includes three steps: identifying existing evidence, identifying and developing theory, and modelling the process and outcomes.[27,31,32] Additionally, we tested the face validity of the PREDOCS Programme. Figure 1 depicts the study flow.

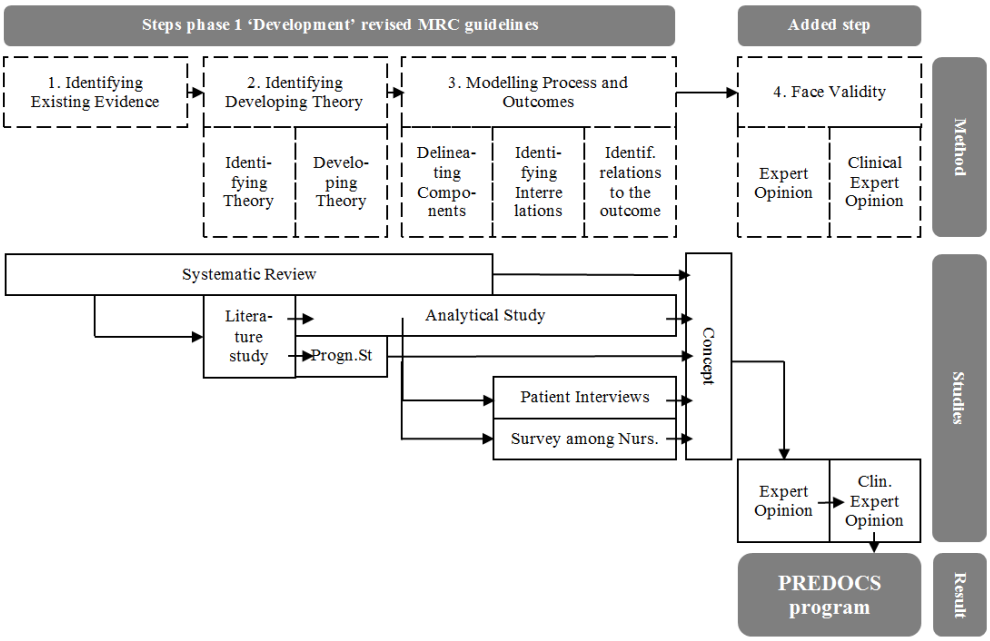

Figure 1 *Flow of study*

In reporting this process, we followed the recently proposed CReDECI reporting criteria concerning the first stage, i.e., development of the intervention (see appendix 2).

An overview of the PREDOCS Programme development process is given in table 1. A team of researchers, consulting experts, cardiac surgeons, registered cardiac surgery nurses, and patients, developed the intervention for PREDOCS Programme'.

Identifying existing evidence

To build on existing evidence, in this first step, studies describing similar interventions must be identified.[27,31,32] Therefore, in a systematic review, we identified studies describing interventions for preparing older patients for a hospital admission for cardiac surgery and the methods that have been used to evaluate these interventions.[33] This enabled us to collect evidence regarding components that can be applied in the preadmission period in older patients who are scheduled for a hospital admission for cardiac surgery (see table 1).

Identifying and developing theory

To provide insight into the rationale leading to the likely process of change in these patients following the PREDOCS Programme, we conducted a second literature review, an analytical study, and a prognostic study.

In this second systematic literature review, we studied possible relationships between the preadmission characteristics of these older patients and the occurrence of postoperative delirium, depression, pressure ulcers, and infection in these patients.[17,34-36] The study flow can be found in appendix 3. We compared the preadmission characteristics of patients who experienced one or more of these four postoperative complications with patients who did not suffer from these complications. In this way, we identified patient characteristics that are related to the occurrence of a postoperative complication.[17,22]

Most studies focus on one or a few patient characteristics and therefore do not reveal the multivariable relations, which are crucial to know in addressing potential factors. Subsequently, we executed an analytical study in which we modelled preadmission patient characteristics related to postoperative complications in a multivariable way. We therefore collected data on these preadmission characteristics in 1,761 patients who were 65 years and older from the Isala Clinic in Zwolle, the Netherlands.

Preadmission patient characteristics related to postoperative complications that were not included in the existing preadmission screening were added to this screening by means of a questionnaire. The Isala Clinic is one of the largest cardiac surgery centres in the Netherlands, where over 1,400 cardiac surgery procedures are performed each year. As part of a continuous data registry for patient management, improvement in the quality of care, and research purposes, pre-, peri-, and postoperative data for all patients undergoing cardiac surgery were prospectively collected between January 1, 2008 and October 30, 2010 in cases in which patients had given informed consent. The local ethical review board approved the study protocol. Preadmission data were collected four weeks prior to the surgery procedure. All patient identifying information was removed before the analyses were conducted. Consequently, we also collected in-hospital data such as surgery and

intensive care unit (ICU) characteristics and the occurrence of postoperative delirium, depression, pressure ulcers, and infection in these patients and calculated the risks.[25,37,38] Using multivariable logistic regression and adjusting for surgical and ICU risks, patient characteristics related to one or more of the four postoperative complications that are potentially modifiable in the preadmission period were identified. The results of this analytical study provided several clues, such as poor eyesight, using a walking stick or walker, or using insoles or a brace, for the best places to start intervening during the preadmission period in these patients. These places to start reveal valuable pieces of theoretical understanding of the likely process of change in these patients.

Additionally, as seen in the literature and according to the patient data, it appeared that in preparing these patients for cardiac surgery, the nurse is confronted with a heterogeneous population with respect to frailty. Therefore, the intervention should include a screening component to identify patients with an increased risk for one or more of the four prevalent postoperative complications. Consequently, we identified predictive patient characteristics that can be noted four weeks before surgery and used to identify older patients with an increased risk for postoperative delirium, depression, pressure ulcers, or infection after cardiac surgery. Following a prognostic research design using the same dataset of 1,761 patients of 65 years and older, we developed prediction models with subsequent scorecards by stepwise backwards variable selection with bootstrap (n=1000) resampling validation.[38]

Modelled process and outcomes

In this third step, an understanding of the intervention and its possible effects must be developed, that is to say: delineating the intervention's components, identifying how they may be interrelated, and understanding how important components may relate to the outcomes.[26,31,32]

First, in delineating the components of the intervention, we compared the evidence on effective preventive interventions derived from our systematic review with the valuable theoretical understanding of the likely process of change in these patients that was obtained from our analytical study. This comparison was performed by the first author (RE) guided by the relationships found in the analytical study, which were categorised by postoperative complication and related to the effective interventions identified from the literature. Second, to identify how these components could be interrelated, in one study, we interviewed patients, and in a second survey study, we asked nurses to reflect on the possible role of nursing care on the development of delirium, depression, pressure ulcers, and infection in these patients. In the first study, we used semi-structured in-depth interviews the day before or at the day of discharge, before the start of the actual discharge procedure. In a convenience sample in three hospitals, nine cardiac surgery patients were asked about their perceived needs before and during their admission. The semi-structured questionnaire was constructed based on literature on the experience and needs of older surgery patients. [39] The data were analysed using the process of hermeneutic interpretation, in which the content, meaning, and significance are combined to understand patient needs

in the context of facing and experiencing a hospital admission for a cardiac surgical procedure.[39] Patients gave informed consent, and all patient identifying information was removed before the qualitative analysis was conducted. In the second study, we used a survey design with a face-validated questionnaire[40,41] to ask 368 nurses from cardiac surgery departments in four Dutch hospitals about their opinions on the prevention, diagnosis, and treatment of postoperative delirium, depression, pressure ulcers, and infection in older cardiac surgery patients. For this survey, we modified a questionnaire that was originally developed by Ely and colleagues[40] to assess the medical community's beliefs and practices regarding delirium in the intensive care unit. Verstraete and colleagues[41] translated this questionnaire into Dutch and ran a subsequent face validity test on a Belgium expert panel and a pilot test among Belgian nurses. In addition to measuring opinions regarding delirium, we modified the questionnaire of Verstraete and colleagues to also measure opinions regarding depression, pressure ulcers, and infection and tested its face validity among cardiac surgery nurses from a large cardiac surgery centre in the Netherlands. Taking into account the differences in the degree of evidence, the results of both studies were used to complement the developed theory in step two, providing insight into the components of the intervention and the interrelationships between these components. This was performed by the first author (RE) in cooperation with the last author (MS) and led to the first draft of the intervention.

Third, to understand how important components may relate to the outcomes, we again looked at the relationships revealed by our analytical studies, but now taking into account the determined interrelationships. Finally, we determined the form in which the intervention is to be performed by the nurse.

Face validity

After completing the three steps of the development phase of the MRC model, we tested the PREDOCS Programme on face validity concerning the content and clinical applicability in a two-stage process. In the first stage, five Dutch national leading nurse experts in the fields of delirium research, depression research, pressure ulcer research, infection research, and cardiac surgery patient education research and one medical expert in anaesthesiology research independently assessed the content of the intervention. Any comments that contradicted the data were discussed independently with each expert by the first author (RE) and further discussed with the other authors. In the second stage, in each of three hospitals, a cardiac surgeon and a cardiac surgery nurse independently commented on the clinical applicability of the intervention. The results were discussed in two sessions with cardiac surgery nurses from three cardiac surgery centres. Comments from both expert rounds were incorporated into the intervention.

Table 1: Process of development of the PREDOCS programme

METHOD				RESULTS		
Development steps (MRC)	***Substeps***	***Approach***	***Derived from***	***Results***	***Conclusions for the intervention***	***CRe-DECI item***
1. Identi-fying existing evidence		Identifying studies that describe interventions for preparing older patients for a hospital admission for cardiac surg.	Systematic review	Multi-component interventions (programs, prehabilitation) are effective in reducing postoperative complications. Disinfection with chlorhexidine combined with immune-enhancing nutritional supplements prevents infection.		1
2. Identi-fying and develo-ping theory	2.1. Identi-fying theory	Identifying preadmission patient characteristics that are associated with postoperative complications	Litera-ture review	Use of resources, having a disability, living status, frequency of weekly social contacts, anxiety, and need for information for the operation or the anaesthesia, level of education, conditions during professional life (including household), history of diseases, number of chronic diseases, and number of preadmission medication prescriptions are associated with a problematic postoperative course.		1
	2.2. Develo-ping theory	Comparison of these preadmission characteristics in patients who experienced one or more of these four postoperative complications with patients who did not suffer from these complications	Analytical study	Postoperative occurrence of *delirium* was associated with living in a nursing home, having insulin-dependent diabetes, and using benzodiazepines. *Depression* was associated with using blind aids, insoles, digoxin, benzodiazepines, pulmonary medication, and diuretics. *Pressure ulcer* was associated with using insoles, depending on a wheelchair, and using diabetes medication in non-insulin-dependent diabetes patients. *Infection* was associated with depending on a wheelchair and using fraxiparin.	Patients should be prepared for the hospital admission in such a way that they can reduce their increased risk	3
		Identifying preadmission predictive patient characteristics	Prognotic study	The nurse is confronted with a heterogeneous population with respect to frailty. Therefore, to predict each postoperative complication (delirium, depression, pressure ulcer, and infection), a scorecard was developed.	Screening patients for an increased risk for one or more of the four prevalent postoperative complications	3

Table 1: Process of development of the PREDOCS programme

	METHOD			RESULTS		
Development steps (MRC)	***Substeps***	***Approach***	***Derived from***	***Results***	***Conclusions for the intervention***	***CRe-DECI item***
3. Modelled process and outcomes	3.1. Delineating the compo-nents	Comparison of effective preventive interventions with the valuable theoretical understanding of the likely process of change in these patients	Syste-matic review Analy-tical study	The amount of information provided in advance of the surgery procedure was too much for most patients to process. This was especially true with regard to the importance of maintaining good nutritional condition, ensuring steady social support from loved ones when entering the hospital, and managing pain after the surgery during the hospital admission.	All patients should be prepared for the hospital admission with regard to maintaining a good nutritional condition, ensuring steady social support from loved ones, and adequately managing pain after the surgery during the hospital admission.	5
	3.2. Identi-fying how compo-nents could be interre-lated	Relating the components to the opinions of nurses and the needs of patients in current practice	Patient inter-views Survey study among nurses	Patients indicated the need for information about what they were going to experience as a patient and what they could and should do as a patient. Most patients and their families wanted to be informed about the risks of postoperative complications The majority of the responding nurses underestimated the incidence of delirium, depression, and pressure ulcer in their department. They did not routinely screen for these conditions. Because they did not screen routinely for these conditions, they underestimated their incidence.	To enhance self-management, information has to be provided on three levels: 1) the procedure itself, 2) the patient's expected experiences, and 3) what the patient can and must do The nursing departments have to be informed when new patients have an increased risk of developing a postoperative complication, and they need to be provided with advice about specific nursing care.	4
	3.3. Identi-fying how importan t compo-nents relate to the outcome	Comparison of the identified interrelations between components with the theoretical understanding of the likely process of change in these patients	Step 3.2 & Analy-tical study	The intervention should consist of three parts: a first general part for all patients, a second part in which high-risk patients are identified, and a third part in which patients with an increased risk are informed specifically about how to prepare themselves for the hospital admission in such a way that they can reduce their increased risk. The intervention should occur during a consult with a nurse two to four weeks prior to the surgical procedure.	The first part is for both frail and non-frail older patients and should include the provision of general information on three levels: 1) the procedure itself, 2) the patient's expected experiences, and 3) what the patient can and must do. This general part should also include guidance on the importance maintaining good nutritional status, ensuring the presence of a steady social support during	2 & 5

Table 1: Process of development of the PREDOCS programme

	METHOD			RESULTS		
Development steps (MRC)	***Substeps***	***Approach***	***Derived from***	***Results***	***Conclusions for the intervention***	***CRe-DECI item***
				In the context of providing continuity of care, the findings from this consult are reported to the nursing team in charge during the patient's hospital admission, along with advice about additional nursing care.	the hospital admission, and asking for adequate pain management after the surgery during the hospital admission.	
Extra step: Face validity	4.1. Expert opi-nion	Feedback of leading experts in the research fields of delirium, depression, pressure ulcer, infection, anaesthesiology, and cardiac surgery patient education	Expert round	Proposals to change medications should not be part of this intervention as this is not a nursing task. The nurse should be trained to guide breathing exercises.	Proposals for a change in medication were removed.	6
	4.2. Cli-nical expert opi-nion	Feedback of cardiac surgeons and cardiac surgery nurses in three hospitals	Clinical expert round	The nurses felt comfortable learning how to guide breathing exercises and felt that they were able to implement the intervention. Cardiac surgeons understood the importance of the intervention.	Nurses were trained by a physiotherapist in how to guide breathing exercises.	6

RESULTS

An overview of the results of the development process leading to the PREDOCS Programme with the accompanying CReDECI-items is presented in table 1.

Identified existing evidence

In the systematic review studying effective preventive interventions, 1,335 initial citations were involved. Of these, only 31 were subjected to critical appraisal. Finally, 23 studies were included, from which a list of interventions was derived that can be applied in the preadmission period. We concluded that multi-component interventions, which include different single interventions, have the strongest effect on preventing postoperative depression, prolonged intensive care unit stays, and hospital stays. Several multi-component interventions proved to be effective. Postoperative infection can best be prevented by disinfection with chlorhexidine combined with immune-enhancing nutritional supplements. No high-quality studies showing effective preventive interventions for postoperative delirium or pressure ulcers in older elective cardiac surgery patients could be identified.[33]

Identified and developed theory

In the second systematic literature review studying the relationships between the preadmission characteristics of older patients scheduled for cardiac surgery and the occurrence of a problematic postoperative course due to postoperative complications, 59 initial citations were incorporated, and only six were included.[17,22,38-42] The study flow is depicted in appendix 3. Patient characteristics from single-outcome studies showing a relationship with the occurrence of postoperative complications can be found in table 1 in the section describing the results of identified theory. From this information, we derived the questionnaire, which we added to the preadmission screening of 1,761 cardiac surgery patients 65 years and older.[35] Subsequently, to obtain a theoretical understanding of the process of change in patients, in an analytical study, we modelled these patient characteristics with each of the four outcomes—postoperative delirium, depression, pressure ulcers, and infection—adjusted for surgery and ICU risks, and we identified potential starting points for the intervention. The associations of each of the four postoperative outcomes with preadmission patient characteristics can be found in table 1 (results of developing theory). The models with crude and adjusted odds ratios are presented in appendix 4.

The scorecards resulting from the subsequent prognostic study, which forms an integral part of the intervention, are presented in part 2 of appendix 5.

Modelled process and outcomes

As described in the previous chapter, this step includes three sub steps: delineating the intervention's components, identifying how they may be interrelated, and understanding how components may relate to the outcomes. Following the first sub step, an important issue proved to be that for most patients, the amount of information given before surgery was too much to remember. This mainly involved trying to take into account the importance of a good nutritional condition, the importance of steady social support from loved ones, and the importance of pain management.

In identifying how these components could be interrelated, from the in-depth interviews with patients exploring their perceived needs before and during the hospital admission, it appeared that most patients had collected information by themselves about the hospitalisation. There were also patients who preferred to ignore the upcoming surgery. Most patients wanted to maintain their own pace in handling the information. In addition to receiving information about the general procedure, important issues that were raised were the need for information about what they were going to experience as a patient and what they can and should do as a patient. One patient, who previously wanted to know nothing, concluded afterwards that he should have wanted to be informed about the procedure and the risk for postoperative complications. Most patients and their families had previously wanted to be informed about these risks.

Two-hundred and fifty cardiac nurses (67.9%) out of 368 from four different hospitals responded to the survey asking their opinion on the prevention, diagnosis, and treatment of these postoperative complications. It appeared that three out of four nurses believed that delirium in elderly cardiac surgery patients is underdiagnosed. In addition, two out of three nurses responded that they do not screen patients routinely for delirium and depression. Only half of the responding nurses mentioned scales or score lists for screening patients on delirium, depression, or pressure ulcers. Here, a negative self-sustaining situation emerged: the majority of the responding nurses admitted that they underestimate the incidence of delirium, depression, and pressure ulcers in their department, yet they do not screen routinely for these conditions. Infection was mostly diagnosed with the support of laboratory tests. Most nurses were able to mention treatments for all four complications. To reduce the incidence of postoperative complications, nurses must first see the necessity for prevention and screening, preferably by being more aware of the increased risk of poor patient outcome.

By better understanding how individual components relate to the outcomes and based on the results described above, we decided that the intervention should consist of three parts: 1) a generic part for all patients, 2) identification of high-risk frail patients, and 3) informing patients with an increased risk on how to specifically prepare themselves for the upcoming hospital admission. The first, generic part is for all older patients (both frail and non-frail), and should include general information on three levels: 1) the procedure itself, 2) the patient's expected experiences, and 3) what the patient can and should do. This part should also include guidance on the importance of good nutrition, arranging the presence

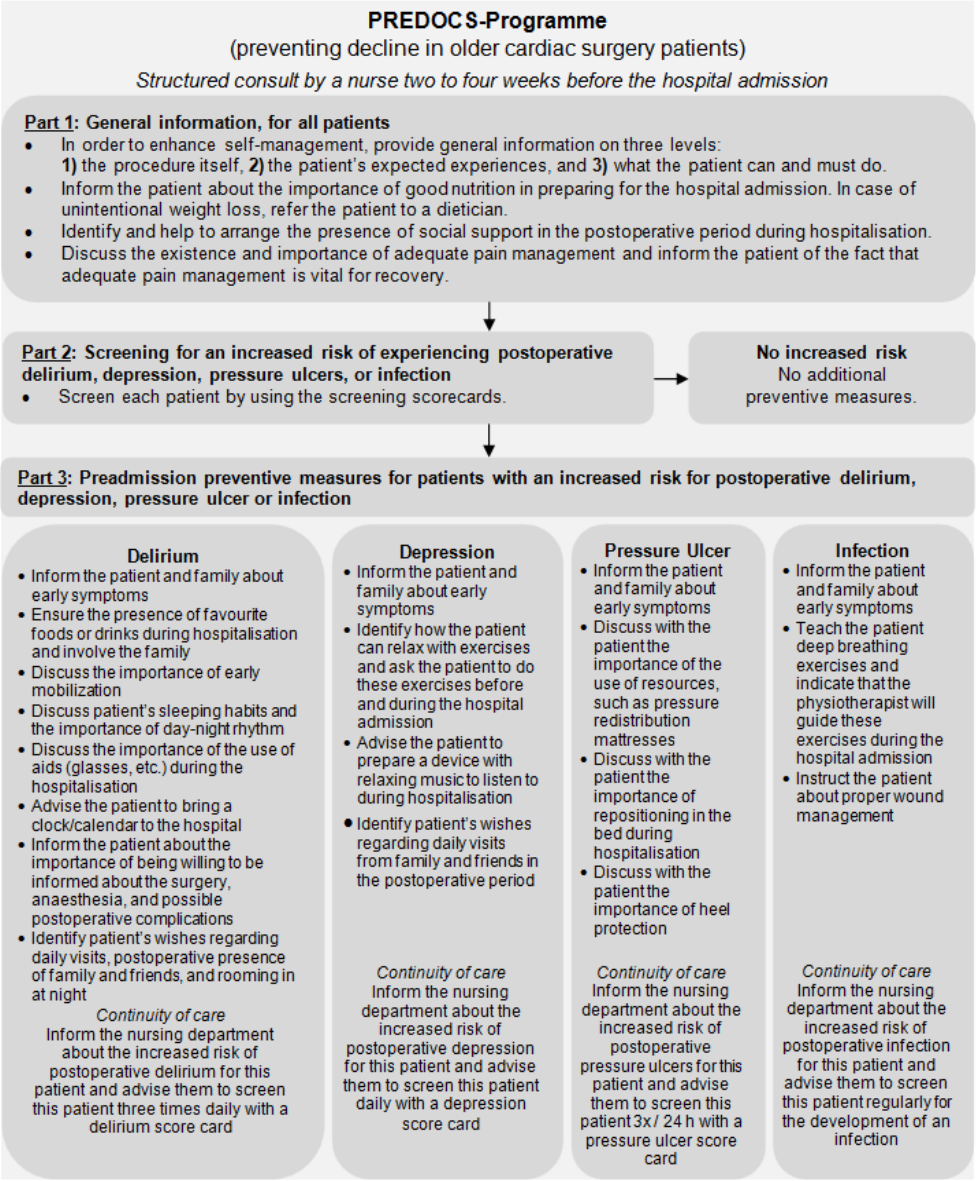

Figure 2 *Flow of the PREDOCS programme for preparing older patients for their hospital admission for cardiac surgery*

of steady social support, and the importance of adequate pain management. It was also decided that the intervention should be given in a consult by the nurse with the patient two to four weeks prior to the surgery procedure. At that early stage, the patient is able to prepare her- or himself for the hospital admission for cardiac surgery. In the context of the

continuity of care, the findings of this consult are reported to the nursing team that is in charge during patient's hospital admission.

Face validity

The results of the first expert round among five Dutch national leading experts concerning the content of the intervention showed that there were some difficulties with the interventions for all identified patient characteristics that were identified in the analytical study. For instance, changing medication is not the responsibility of the nurse and should be performed by the prescribing physician. Furthermore, the intervening action, teaching the patient to adequately perform breathing exercises, should be performed by a skilled person, and the nurse should be appropriately trained. The results of the second expert round among cardiac surgeons and the cardiac surgery nurses concerning the clinical applicability of the intervention showed that they understand its importance. In accordance with the responses from the national experts, the nurses responded that they did not feel well prepared to implement all aspects of the intervention. However, they felt comfortable learning the necessary information and expected that they could implement the intervention after appropriate training. The flow of the intervention is depicted in figure 2, and a complete overview of the intervention is provided in appendix 5.

DISCUSSION

In this study, following the revised MRC guidelines for conducting a series of both qualitative and quantitative studies to form an extensive base, we developed a multi-component intervention to be applied by nurses with older patients who will be admitted to the hospital for cardiac surgery: the PREDOCS Programme. With the PREDOCS Programme, two to four weeks before the cardiac surgery procedure, vulnerable patients are identified and supported to reduce their increased risk of postoperative delirium, depression, pressure ulcer, or infection.

Most studies in the literature regarding the preparation of patients for cardiac surgery report on preoperative interventions and not preadmission interventions.[6,13-16,42] As seen in a recent study concerning a multi-component education intervention conducted two to three days before surgery to reduce anxiety and improve recovery among Chinese cardiac surgery patients, preoperative education is effective in reducing anxiety and depression.[43] Another example involves a proposal for a systematic approach to careful patient selection and preparation during the preoperative evaluation period to minimise morbidity and mortality in patients scheduled for coronary artery bypass grafting surgery.[44] In contrast, there are a few studies focussing on the preadmission period, such as a study showing that a cognitive-behavioural intervention (the HeartOp Programme) involving routine nurse counselling for patients awaiting first-time elective coronary artery bypass grafting surgery

reduces depression and improves physical functioning.[20] Another study involves the 'Fit For Surgery' Programme, which includes pre-operative appointments with a cardiac homecare nurse and shows a reduction in overall healthcare utilisation.[21,45,46]

To evaluate the present results, a few additional points must be considered. First, we estimated that going through this first phase of intervention development for the revised MRC guidelines would lead to a completed intervention. However, at several stages in the PREDOCS protocol, indications to change medication prescriptions arise, and nurses cannot change medication without consulting a physician. Additionally, we suspect that not all patient characteristics that predict the four postoperative complications and their possible preventive measures have been identified because they simply were not studied and therefore could not be identified from the literature. Therefore, we added an extra step of testing the face validity in two rounds. In the first round, we consulted national research experts, and in the second round, we consulted clinicians and asked them to evaluate the text of the intervention at that stage. As expected, they complemented the level of detail included.

Second, in this study, we limited ourselves to the preadmission period only, but it is plausible that nurses in the wards will take into account the fact that part of the patient population was identified as being at risk for one or more of the four postoperative complications and therefore will take preventive action. From the viewpoint of a Programme, these preventive nursing actions *during* the admission based on the results of the preadmission PREDOCS Programme should be taken into account. In this study, we did not elaborate on these nursing follow-up actions, and this must be considered when applying our results to nursing practice.

Third, some argue that the primary-care physician, the surgeon, and the nurses should be alert to the development of postoperative complications and that such an in depth preoperative preparation could possibly tire the patient more than it helps. However, this reasoning reflects a reactive approach rather than a proactive approach. Given the improvements in surgical techniques and anaesthetic procedures combined with the rapidly growing number of older people, cardiac surgical procedures are applied to greater numbers of more vulnerable patients. The population is changing. As evidenced by the high number of postoperative complications, due to their vulnerability, the self-management skills in vulnerable patients are often diminished. The approach of the PREDOCS Programme is to provide the nurse with an intervention to guide the vulnerable older patient in improving her or his self-management in such a way that the patient is able to actively work on decreasing the risk on postoperative delirium, depression, pressure ulcers, or infection before the actual admission to the hospital.

Fourth, although we used a carefully phased approach following the revised guidelines of the MRC, there is no conclusive path to follow when developing a single-component intervention and even less guidance for developing a multi-component complex intervention. During the development process, we made many decisions, each based on as

much available evidence as possible and the knowledge of experts, nurses, and patients. However, there were some limitations. For instance, we used a convenience sample for the patient interviews using a questionnaire that was only tested for face validity, and we collected the data of 1,761 older cardiac surgery patients for both our analytical and our prognostic study from a single heart centre. These facts have to be taken into account when generalising our findings. To our knowledge, however, this is the first attempt to collect and translate evidence to clinical practice in a comprehensive manner with the goal of reducing postoperative delirium, depression, pressure ulcers, and infection. This carefully phased approach provides a robust base for the expected effectiveness of the intervention.

Conclusion

Starting with the geriatric paradigm in mind, with this study, we provide an integral evidence-based multi-component nursing intervention for application in the preadmission period with the aim of improving patients' physical and psychosocial conditions to reduce the risk of postoperative complications in high-risk frail older cardiac surgery patients. Two to four weeks before the surgery procedure, during a consult, the nurse determines whether the patient has an increased risk of experiencing delirium, depression, pressure ulcer, or infection. Subsequently, patients with an increased risk receive information on additional actions that will give them an opportunity to reduce their risk.

Following the revised MRC guidelines, an extended stepwise multi-method procedure was used to develop the multi-component nursing intervention for preparing older patients for cardiac surgery. By creating transparency in the assumed working mechanism and providing a detailed description of the intervention, which both are often lacking from multi-component intervention studies, we enhance the validity of the PREDOCS Programme.

We recognise that these guidelines remain to be tested; therefore, following the MRC guidelines, a feasibility study is being developed to evaluate the PREDOCS Programme in clinical practice.

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APPENDIX 1

Evolution of the Medical Research Council guidelines of complex interventions

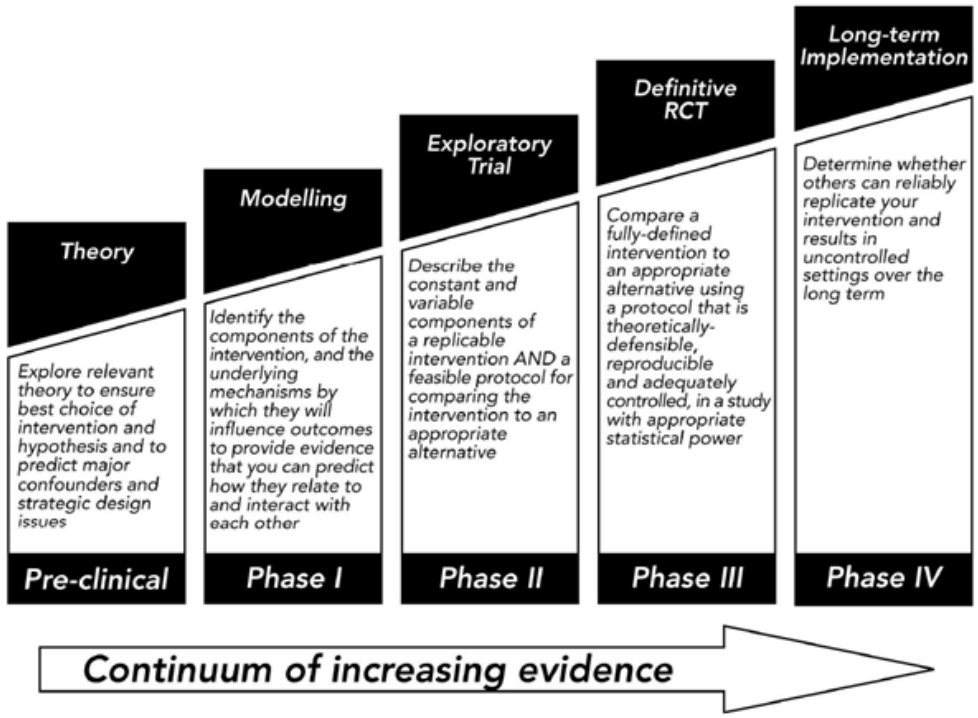


Figure 1 *Framework for trials of complex interventions, original version, which is based on the linear sequenced phases of drug development*[30]

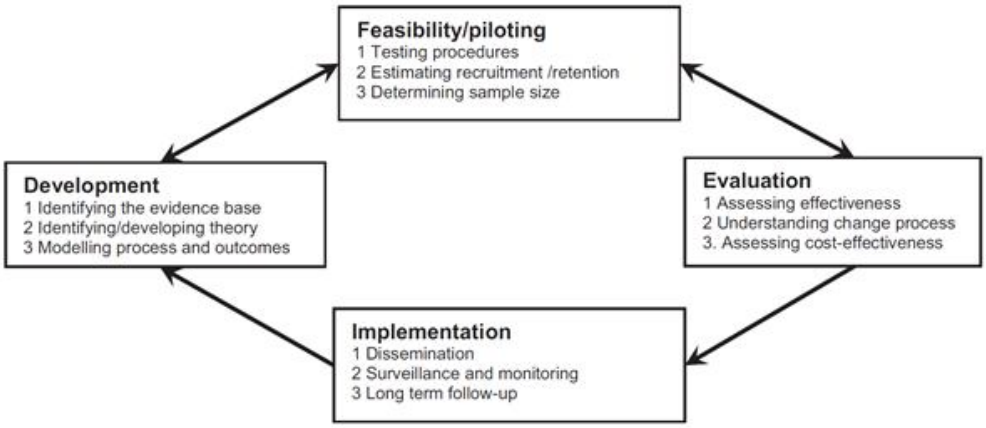


Figure 2 *Key elements of the development and evaluation process of complex interventions, revised version, which is described according to cyclical phases* [27,31,32]

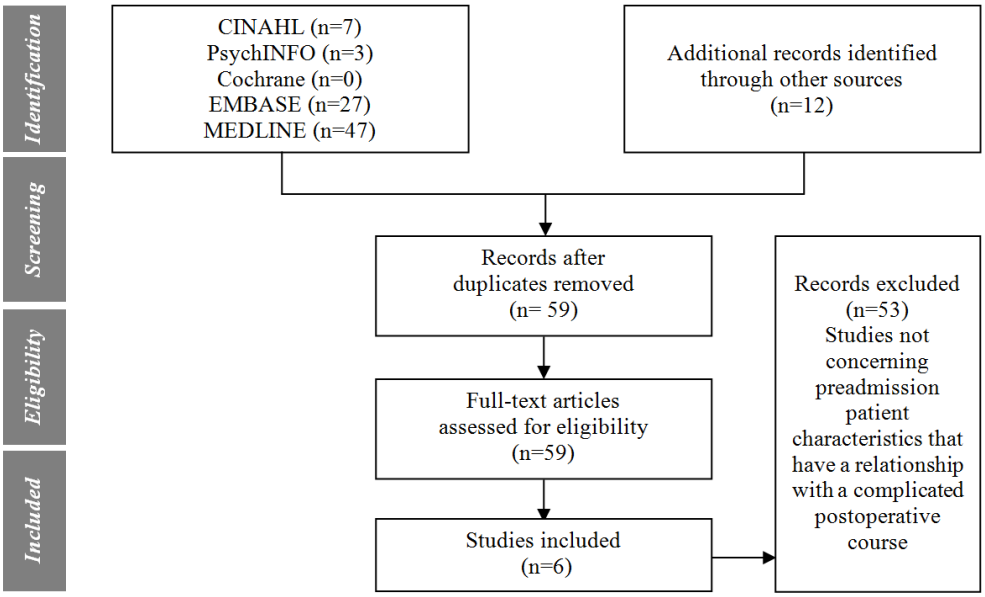
APPENDIX 2

CReDECI checklist

First stage – Development [29]

1. Description of the intervention's underlying theoretical considerations
2. Description of all components of the intervention
3. Rationale for the selection of the intervention's components
4. Illustration of any intended interactions between different components
5. Rationale for the aim/essential functions of the intervention's components, including the evidence about whether the components are appropriate for achieving this goal
6. Consideration of contextual factors and determinants of the setting in the modelling of the intervention

APPENDIX 3



Flowchart of the systematic literature review of studies on the relationships between the preadmission characteristics of older patients who are scheduled for a hospital admission for cardiac surgery and the occurrence of a problematic postoperative course due to postoperative complications

APPENDIX 4 ***Delirium, Depression, Pressure Ulcer, and Infection risk as a function of preadmission patient characteristics n=1.761***

	Delirium		**Depression**		**Pressure Ulcer**		**Infection**	
Preadmission Patient Characteristics¶	*Crude* OR (95%CI)†*	*Adjusted** OR (95%CI)†*	*Crude* OR(95%CI)†*	*Adjusted‡ OR(95%CI)†*	*Crude* OR (95%CI)†*	*Adjustedϕ OR (95%CI)†*	*Crude* OR (95%CI)†*	*Adjusted§ OR (95%CI)†*
Walking stick or walker	2.2 (2.1-2.4)	1.6 (1.5-1.8)			1.7 (1.5-1.8)	1.3 (1.2-1.5)	1.7 (1.6-1.9)	1.4 (1.3-1.6)
Wheelchair					2.3 (2.0-2.5)	2.2 (2.0-2.4)	2.5 (2.3-2.7)	2.1 (1.9-2.4)
Orthopaedic Shoes			0.6 (0.4-0.8)	0.6 (0.4-0.8)	1.4 (1.2-1.6)	1.5 (1.3-1.7)	0.3 (0.0-0.6)	0.3 (0.0-0.6)
Uses insoles	1.7 (1.5-1.8)	1.7 (1.5-1.9)	2.5 (2.4-2.7)	2.5 (2.3-2.6)	12.5 (12.0-13.1)	14.8 (14.2-15.4)		
Uses brace (knee, wrist)	2.6 (2.3-3.0)	2.1 (1.7-2.5)	2.3 (1.9-2.6)	2.6 (2.2-2.9)				
Uses blind aids			3.6 (3.2-4.1)	3.6 (3.2-4.1)				
Poor eyesight	5.2 (4.7-5.7)	5.9 (5.4-6.3)						
Hearing aid					1.3 (1.2-1.5)	1.3 (1.1-1.4)	0.7 (0.5-0.8)	0.6 (0.4-0.8)
Religious	1.4 (1.3-1.6)	1.3 (1.1-1.4)						
Contacts mostly with fellow believers	1.4 (1.2-1.5)	1.3 (1.1-1.4)	1.4 (1.2-1.5)	1.3 (1.1-1.4)	1.4 (1.2-1.5)	1.3 (1.1-1.4)		
Single	1.4 (1.3-1.6)	1.4 (1.2-1.5)						
Widow(er)							0.5 (0.3-0.7)	0.5 (0.3-0.7)
Living in a serviced apartment	0.8 (0.6-1.0)	0.7 (0.4-0.9)			2.2 (2.0-2.4)	2.2 (2.0-2.5)		
Living in nursing home	2.0 (1.7-2.3)	2.3 (2.1-2.6)						
Living in an elderly centre							0.9 (0.5-1.3)	0.5 (0.1-0.9)
Feels fear for the surgery with anaesthesia			1.2 (1.1-1.4)	1.2 (1.1-1.4)				
Would like information on the anaesthetic	0.7 (0.5-0.8)	0.7 (0.5-0.8)						
Neurological dysfunc. dis.	1.5 (1.3-1.7)	1.5 (1.3-1.7)						
Stroke or TIA in the past	1.7 (1.5-1.8)	1.9 (1.7-2.0)						
Pulmonary hypertension					0.4 (0.2-0.6)	0.3 (0.1-0.6)		
Renal impairment	1.4 (1.2-1.5)	1.3 (1.1-1.4)						
Hepatic impairment					3.1 (2.8-3.4)	3.8 (3.5-4.1)		
Hypothyroidism	0.7 (0.5-0.9)	0.6 (0.4-0.8)						
History of stomach prob.			1.3 (1.2-1.5)	1.4 (1.2-1.5)	1.3 (1.1-1.4)	1.4 (1.2-1.5)		
Insulin-dependent diabetes	1.6 (1.5-1.8)	1.7 (1.6-1.9)	1.3 (1.2-1.5)	1.4 (1.2-1.5)				
Non-insulin-dep. diabetes					3.2 (3.0-3.4)	3.9 (3.7-4.2)		

APPENDIX 4 ***Delirium, Depression, Pressure Ulcer, and Infection risk as a function of preadmission patient characteristics n=1.761***

	Delirium		Depression		Pressure Ulcer		Infection	
Preadmission Patient Characteristics¶	*Crude* OR (95%CI)†*	*Adjusted** OR (95%CI)†*	*Crude* OR(95%CI)†*	*Adjusted‡ OR(95%CI)†*	*Crude* OR (95%CI)†*	*Adjustedϕ OR (95%CI)†*	*Crude* OR (95%CI)†*	*Adjusted§ OR (95%CI)†*
Preadmission medication use								
Beta blockers	0.7 (0.6-0.9)	0.9 (0.7-1.0)	0.7 (0.6-0.9)	0.7 (0.6-0.9)			0.6 (0.5-0.8)	0.7 (0.5-0.8)
Plavix							0.5 (0.3-0.7)	0.5 (0.3-0.7)
Cholesterol-lowering drugs	0.8 (0.6-0.9)	0.8 (0.6-0.9)						
Ca antagonist	0.8 (0.6-0.9)	0.8 (0.7-1.0)	0.8 (0.6-0.9)	0.8 (0.7-1.0)			0.6 (0.5-0.8)	0.6 (0.5-0.8)
Benzodiazepine	1.6 (1.5-1.8)	1.7 (1.5-1.8)	1.6 (1.4-1.7)	1.5 (1.3-1.6)				
Lipid lowering drugs					0.7 (0.5-0.9)	0.8 (0.6-0.9)		
Pulmonary medication	0.8 (0.6-0.9)	0.8 (0.6-0.9)	1.4 (1.2-1.6)	1.4 (1.2-1.6)	1.3 (1.2-1.5)	1.4 (1.2-1.6)		
Diuretics			1.4 (1.3-1.6)	1.4 (1.2-1.5)			1.8 (1.6-1.9)	1.7 (1.6-1.9)
Fraxiparin			0.8 (0.6-0.9)	0.7 (0.6-0.9)	1.7 (1.5-1.9)	1.8 (1.6-1.9)		
Coumarins					1.5 (1.3-1.6)	1.3 (1.1-1.5)		
Digoxin			1.6 (1.4-1.8)	1.5 (1.3-1.7)				
Synthroid (Thyrax)					0.4 (0.2-0.6)	0.4 (0.1-0.6)		

¶ Preadmission Patient Characteristics that are significantly related to one or more of the four postoperative outcomes

*) Preadmission patient characteristics in the social, psychological, and physical domains of functioning[17,22 34-37]

**) Adjusted for age, gender, surgery and ICU risks, and adverse events during admission (depression, pressure ulcers, and infection)

‡) Adjusted for age, gender, surgery and ICU risks, and adverse events during admission (delirium, pressure ulcers, and infection)

ϕ) Adjusted for age, gender, surgery and ICU risks, and adverse events during admission (delirium, depression, and infection)

§) Adjusted for age, gender, surgery and ICU risks, and adverse events during admission (delirium, depression, and pressure ulcer)

†) Odds ratios and the accompanying 95% confidence intervals are pooled measures (based on Rubin's Rule) of the five datasets

APPENDIX 5

The PREDOCS Programme

This Programme contains interventions to prevent the occurrence of delirium, depression, pressure ulcers, and infection in the phase after cardiac surgery in patients 65 years and older. The timing of the application is two to four weeks before the surgery procedure in a nursing consultation.
Afterwards, after receiving consent from the patient, all collected patient information should be transferred to the nurses in the hospital, either electronically or by paper patient records.

Content

Part 1 General information applicable to all patients

- Specify the general information to the patient so that it takes place on three levels:
  1) The procedure (clinical path itself)
  2) The patient's expected experiences
  3) What the patient can and must do
  It is important to distinguish the information using these three levels. (This enhances the self-management of the patient.)
- Inform the patient about the necessity of maintaining good nutritional condition prior to a hospital admission for cardiac surgery.
  Assign the patient to a dietician for unintentional weight loss (usually caused by loss of appetite due to illness).
- Support the single patient or the patient with a social environment that is not (yet) ready to support the patient after the hospitalisation. Support by making an inventory of social contacts and opportunities to enable them. If necessary, a temporary guest place in a care or nursing home can be requested.
- Specify that the patient may experience pain, and that pain treatment is available. Discuss with the patient that adequate pain treatment is necessary for recovery after surgery. After the operation, the patient has to indicate when she or he feels pain and especially if it is not tolerable.

Part 2 Screen patients for being at risk of experiencing Delirium, Depression, Pressure Ulcer, or Infection in the postoperative phase.

Use the screening score cards and test whether the patients have an increased risk.

Delirium Risk Score Card	**Points**
Experienced delirium previously	2
Alzheimer's diagnosis	2
Uses a stick or walker	2
Logistic EuroSCORE† risk above 20%	1
Receives support from family / friends (informal care) when living alone or not actively supported by the partner	1
Age over 70 years	1
History of Stroke and /or TIA	1
Use of benzodiazepines	1
Total (an increased risk of delirium is 3 or higher)	

†) The European System for Cardiac Operative Risk Evaluation (EuroSCORE) was developed in the eighties for predicting 30-day mortality after cardiac surgery. In the meantime, with improved cardiac surgery techniques, the mortality rates have been minimised. Currently, frail patients can undergo a cardiac surgery procedure with a low mortality risk, but they can have an increased risk of postoperative complications such as delirium, depression, pressure ulcer, and infection. In several studies, the EuroSCORE has been validated for predicting a prolonged intensive care unit (ICU) stay for patients scheduled for cardiac surgery. Prolonged (ICU) stay is then used as a proxy for complications occurring during surgery and intensive care unit stay. [37]

Depression Risk Score Card	**Points**
Use of insoles	3
Deaf	2
Female	1
Use of benzodiazepines	1
Total (an increased risk of depression is 2 or higher)	

Pressure Ulcer Risk Score Card	**Points**
History of Tricuspid insufficiency	5
Physically limited *	3
Single	3
Logistic EuroSCORE risk above 20%	2
Use of Fraxiparin	2
Renal impairment	1
Total (an increased risk of pressure ulcer is 3 or higher)	

*) In the development study for this scorecard, the patient was assessed for a disability. The response categories were: 'deaf', 'blind', 'physically limited', and 'intellectual disability'. Physically limited appeared to be predictive for the occurrence of a postoperative pressure ulcer.

Infection Risk Score Card	**Points**
History of Tricuspid insufficiency	3
Logistic EuroSCORE risk above 20%	2
Use of diuretics	2
Total (an increased risk of infection is 3 or higher)	

Part 3 Preventive measures for patients with increased risks

3a Preventive measures for patients with an increased risk of postoperative Delirium
In patients vulnerable for delirium:

- Inform the patient and family to watch, together with the nurses and doctors, for symptoms of delirium and if necessary to inform the nurse in time. (Self-management by the patient and his or her relatives contribute to a successful completion of the postoperative period in the hospital.)
  The patient can recognise the beginnings of delirium by noticing an increase in forgetfulness, slowly experiencing a type of a haze, feeling fear, and sometimes feel excited. If delirium continues, then the patient lives in a haze (a bad dream) and sees, hears, or feels strange things. (Patients with delirium present with a combination of cognitive problems, varying levels of consciousness, and changes in sleep-wake pattern, alternating restlessness (often accompanied by anxiety and excitement), hallucinations (dreamlike perception of things that do not exist in reality), and other abnormalities in perception.)

- In the context of the prevention of malnutrition and dehydration, identify the patient's favourite foods and drinks and advise the patient and family to provide these items, in consultation with the nursing staff, and have those available 24 hours a day during the admission. In addition, the family is invited to regularly offer these items to the patient during the admission.
- Discuss with the patient that immobility longer than necessary can harm the patient. Discuss with the patient the importance of having a good position in bed and doing active or passive exercises.
- To control sleeping problems, ask the patient about his/her sleeping habits. Advise the patient and family to continue these habits as closely as possible within the routine in the hospital and to discuss this with the nurses. Ensure that a proper distinction between day and night is clear to the patient, e.g., changing for the night and reducing stimuli during the night.
- Make sure the patient uses her or his aids (glasses, hearing aid, walking stick, etc.) and discuss the importance of using these aids, especially during the period of hospital admission. Discuss this with the family to ensure that the patient has these aids available for use in the hospital.
- Encourage the patient to have a private clock and / or calendar so they can orientate themselves.
- Emphasise that the patient should welcome information about the surgery and the anaesthesia. The patient must have an idea of how to address complications such as delirium. (Patients aged 65 years and older who are mentally well prepared for a hospital admission for cardiac surgery are much less likely to develop a complication after surgery, and when a complication occurs, it is less complicated.)
- Discuss with the patient the possibilities for daily visits from family and friends. Discuss with the family the importance of the regular presence of a trusted person in the postoperative period. Explain the occurrence of delirium in relation to disorientation. Ask the family if they may be contacted overnight when something happens to the patient (such as delirium).

Continuity of care to the ward

Report that the patient in question is at risk of experiencing delirium in the postoperative period and that this could be a serious potential barrier to postoperative recovery. Indicate that these patients should be screened for delirium (e.g., Delirium Observation Screening (DOS)) postoperatively (3x per 24 h). If they test positive during the screening or are suspected of exhibiting delirium, they should be sent for diagnosis and treatment (Haloperidol), and any physical causes should be identified and treated (e.g., infection, specific low blood levels, constipation, urinary retention).

3b Preventive measures for patients with an increased risk of postoperative depression
In patients vulnerable for depression

- Discuss with the patient how he or she usually relaxes and how to apply this in the hospital. (Relaxing exercises gives the patient a tool to control stress and anxiety.)
- Advise the patient to prepare a device with relaxing music (MP3 player or similar) prior to the hospitalisation and to bring it to the hospital. (Relaxing gives the patient a tool to control stress and anxiety.)
- Discuss with the patient the possibilities of arranging steady daily visits from family and friends.
- Instruct the patient and family to watch, together with the nurses and doctors, for symptoms of complications and inform the nurse if necessary. (Self-management by the patient and his or her relatives helps with the successful completion of the postoperative phase.) The patient may notice the following beginning signs of depression: feeling down, unable to enjoy anything, inability to concentrate and loss of appetite. (Patients with depression present with a depressed mood and loss of interest, positivity, or enthusiasm, sometimes including guilt, low self-worth, disturbed sleep patterns, lack of appetite, low energy, and low concentration.)

Continuity of care to the ward
Report that the patient in question is at risk for depression in the postoperative period and that this could be a serious potential barrier to postoperative recovery. Emphasise that the patient should be screened for depression (with a screening tool used by the ward). With a positive screening or suspicion of depression, the geriatrician or physician must be informed and asked for a diagnosis and treatment.

3c Preventive measures for patients with an increased risk of postoperative pressure ulcers
In patients vulnerable to pressure ulcer

- Instruct the patient and family to watch, together with the nurses and doctors, for signs of stage 1 pressure ulcers (no timely change of position in the bed and appearance of non-blanchable redness on the heels, sacrum, elbow, or shoulder when lying on the back and ankle, knee, hip, and shoulder when lying on the side) and to notify the nurses if necessary. (Self-management by the patient and the family contributes to successful completion of the postoperative phase.)

Continuity of care to the ward
Report that the patient in question is at risk for developing a postoperative pressure ulcer and that this could be a serious potential barrier to the postoperative recovery. Also, indicate that this patient should be given priority for pressure ulcer prevention, even if seriously ill after surgery, and that means and materials for this patient must be deployed. As soon as the patient leaves the ICU or operating room, immediately start using a

pressure-reducing mattress so the patient does not have to be transferred again onto such a mattress when entering the ward after surgery. Place the heels free as long as the patient is not mobile. Change the patient's position in the bed every 3 to 4 hours if necessary. Report that for this patient, the risk categories should be scored postoperatively (3x per 24 h), and the accompanied risk prevention measures must be taken (such as indicated in the European Pressure Ulcer Advisory Panel guideline).

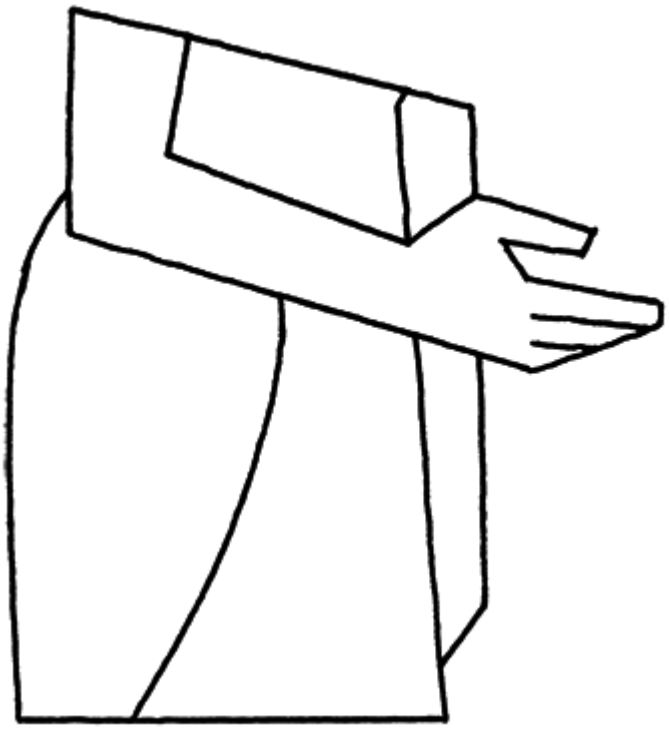
3d Preventive measures for patients with an increased risk of postoperative infection
In patients vulnerable to infection

- Teach the patient breathing exercises, and report that together with the physiotherapist, if necessary, the patient will do these exercises after the operation. (Breathing exercises help avoid pneumonia caused by a lung infection.)
- Instruct the patient and family to watch, together with the nurses and doctors, for signs of a complication and if necessary to inform the nurse. (Self-management by the patient and her or his family contribute to the successful completion of the postoperative phase.) The patient may be the first to notice an initial infection because she or he is in pain (the surgical wounds, respiratory tract, and bladder), feels very uncomfortable or very ill, and is not mobile. (The most common infections in elderly cardiac surgery patients are infections of surgical wounds, the bronchi, lungs, and bladder.)
- Instruct the patient not to touch the wound with the hands and not to wash the wound with soap, but just to wash the wound with tap water and pat the wound dry afterwards.

Continuity of care to the ward
Report that the patient in question is at risk of developing an infection postoperatively and that an infection is a serious potential barrier to the postoperative recovery. Indicate that proper nutrition and the existing decontamination policy (0.12% chlorhexidine gluconate (CHX)) is effective at preventing infections.

Chapter 6

Feasibility of a nursing intervention to prepare frail older patients for cardiac surgery: a mixed methods study



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ABSTRACT

Background: Given the growing number of vulnerable, older cardiac surgery patients, the preadmission PREDOCS programme was developed to reduce the incidence of postoperative complications. Before the clinical effects of such a complex multicomponent intervention can be evaluated, the feasibility needs to be determined to detect possible problems with the acceptability, compliance and delivery of the intervention.

Aim: To test the PREDOCS programme on its feasibility and estimate theoretical cost savings.

Methods: In a mixed-methods multicentre study, the MRC guidelines concerning testing feasibility were followed, and theoretical cost savings were calculated. We used data from interviews and the continuous data registry at three hospitals. The results were reported following the criteria for reporting the feasibility of complex interventions (CReDECI).

Results: Seventy of the 114 eligible patients completed the intervention and provided full data. Patients were equally satisfied with the usual care and the PREDOCS programme. The involved nurses were satisfied with the tools for guiding patients to reduce their risk of postoperative complications and considered the PREDOCS programme as complementary to usual care. Integrating PREDOCS into current hospital structures appeared to be difficult. Both patients and nurses indicated that the additional consult was tiresome for the patient. The PREDOCS programme will be cost-effective when postoperative complications are prevented in six to sixteen of 1,000 cardiac surgery patients.

Conclusions: The PREDOCS programme is feasible to use in clinical practice but should be built into the hospital's cardiac surgery pathway or applied in home care.

KEYWORDS

Feasibility, Frailty, Older People, Cardiac Surgery, Prevention, Postoperative Complications

INTRODUCTION

The share of older people in the western population is rapidly growing. Additionally, improvements in cardiac surgical techniques and anaesthetic procedures now allow surgery even in frail patients.[1-4] Consequently, increasingly older, sicker, and higher-risk patients undergo cardiac surgery. Although frail older patients can now safely undergo the surgical procedure, they are at high risk of developing postoperative complications, including delirium (14,7% to 46.0% [5,6]), depression (10,0% to 37.7% [7,8]), pressure ulcers (10.6% to 18% [9,10]) and nosocomial infections (8.3% to 54.5% [11-14]). These complications are associated with functional and cognitive decline and a decrease in quality of life (QoL) and wellbeing after discharge[15], and they significantly increase hospital costs.[16-20]

Many older patients scheduled for cardiac surgery present with multiple comorbid health problems, most of which are multifactorial in etiology. This means that more than one risk factor is related to the outcome[21,22] and more postoperative complications can occur in one vulnerable patient.[21] Therefore, an effective intervention should properly address this multifactorial origin.[22]

We developed a multi-component preadmission nursing intervention called "PREvention Decline in Older Cardiac Surgery patients" (PREDOCS) to better prepare older patients for elective cardiac surgery and to prevent postoperative complications. The PREDOCS programme includes a comprehensive geriatric nursing approach aimed to prevent four frequently occurring postoperative complications: delirium, depression, pressure ulcers and infections. The programme can be offered to patients 65 years and older who are scheduled for cardiac surgery. It consists of one nursing consult, two to four weeks prior to surgery.

For the development and evaluation of this multi-component complex intervention, we used the revised guidelines of the British Medical Research Council (MRC) (Appendix 1). The MRC defines multi-component or complex interventions as interventions that have multiple possible interacting components, with one or more outcomes.[23,24] In a previous study, we reported on the development of this intervention in accordance with phase one of the MRC guidelines.[25] Here, we report on the feasibility of the PREDOCS programme.

Before the PREDOCS programme can be evaluated on its intended reduction of postoperative complications, the feasibility (e.g., acceptability) and recruitment and retention of participants should be investigated.[25] Additionally, to explore the potential cost-effectiveness of the PREDOCS programme, we estimated the theoretical cost savings from reductions in the cost for care and treatment of postoperative complications. Therefore, the purpose of this study was to test the newly developed PREDOCS programme on its feasibility and potential challenges in clinical practice and to estimate the theoretical cost savings.

METHODS

A multicentre study with a 'mixed-methods' approach[26] was used to test the feasibility of the PREDOCS intervention. The MRC defines phase-two feasibility testing as follows: testing procedures, estimating recruitment and retention and determining the sample size. Qualitative methods (interviews with patients, nurses and nursing managers) were used to assess acceptability. Quantitative methods (satisfaction ratings) were used to assess recruitment and retention and to calculate estimated cost-savings.

Participating centres - Two large cardiac surgery centres and one university hospital in the Netherlands participated in the assessment of feasibility. The cardiac surgery centres were St. Antonius Hospital in Nieuwegein and the Isala Clinics in Zwolle; where over 1,700 and 1,400 cardiac surgeries are performed each year, respectively. In the University Medical Centre of Utrecht, over 800 cardiac surgeries are performed each year.

Patients - Participating patients were 65 years or older, planned for cardiac surgery, and were able to visit the preoperative screening programme. Both patients with and without an increased risk were included because selection of patients at risk for a postoperative complication is a part of the PREDOCS programme. Patients were excluded if they were unable to speak Dutch, participated in another study at the same time, needed preoperative intubation or were unable to give informed consent. Patients currently diagnosed with mental illness or an infection or who had experienced heart or lung transplantation were also excluded.

Procedures - At the start of the study, six nurses, two at each hospital, received training in providing the intervention during a single four-hour session. This training included an introduction to the PREDOCS programme, a physiotherapist explaining how to instruct the patients to perform breathing exercises, and application of the PREDOCS programme to the hospital structure. The PREDOCS programme was added to the existing preoperative screening programme at the preoperative clinic, where the patient typically visits one to four weeks before admission to the hospital. The review board of the Isala Clinics was appointed as the principal review board for this multiple centre study and approved the study protocol. All patient-identifying information was removed before the analyses were conducted. The flow of the mixed-methods approach is depicted in Figure 1.

Testing procedures and data collection

Baseline characteristics were collected, including age, gender, type of operation, body mass index, chronic diseases, use of resources, educational level, social status, and any handicaps. Furthermore, the time between receiving the PREDOCS programme and the surgery was registered.

To investigate how satisfied patients were with the intervention, patients were contacted by telephone at home by a research nurse or the first author (RE) within 7 days after discharge and were asked six questions. The questionnaires used for structuring the telephone interviews can be found in Appendix 2. Satisfaction was defined as the degree of

meeting realistic expectations.[27-29] Following this definition, three open-ended questions were asked focusing on the expectations about the following: 1) general preparation for the surgery, 2) usual care, and 3) the PREDOCS programme. Additionally, a closed question regarding a satisfaction rating on a 10-point scale was asked, with higher scores indicating higher levels of satisfaction.

At each hospital, two nurses and one nurse manager were involved in the study. In semi-structured interviews[30] conducted halfway and at the end of the recruitment period, the nurses were asked to indicate if they thought the intervention was feasible. The two topics discussed were strengths and limitations during the implementation and suggestions to further improve the intervention. The questionnaires used for structuring the interviews with the nurses and the nurse managers can be found in Appendices 3 and 4. NVivo 7.0 was used for coding the interviews. Experiences were first classified and coded on the basis of the answers given. Then, codes were reduced into themes and described.[31]

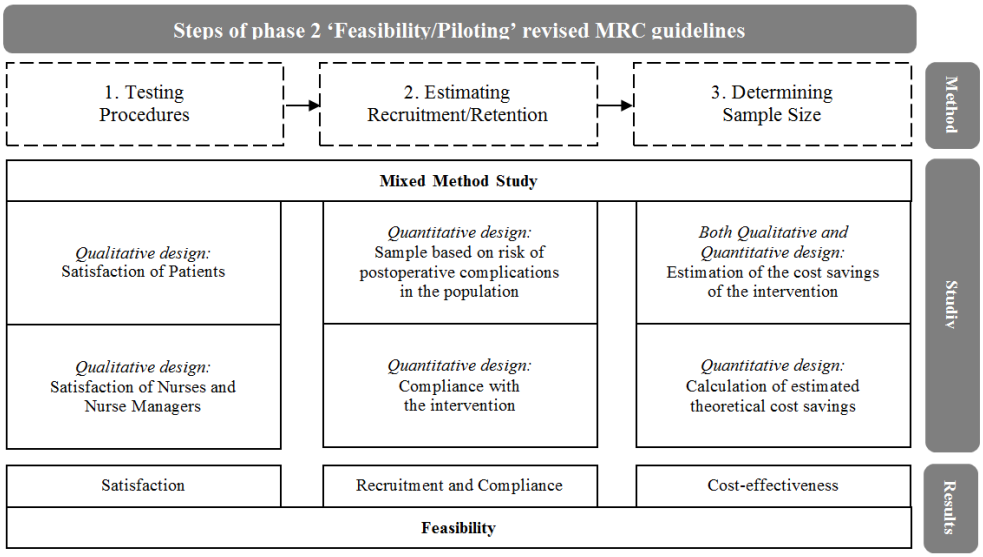

Figure 1 *Flow of the mixed-methods approach*

Estimating recruitment and retention

Because we do not know the baseline rate of retention of similar nursing interventions, we refrained from a formal sample size calculation, and we calculated a sample size based on the observed incidences of delirium (18%), depression (15%), pressure ulcers (11%), and infections (7.5%) amongst 1,761 older cardiac surgery patients at the Isala Clinics.[32] Based on these measured incidences, four to seven of 30 patients were expected to have an increased risk to develop delirium, three to five patients to develop depression, two to five patients to develop a pressure ulcer and one to four patients to develop an infection. Consequently, a sample of 90 patients was selected, including 30 patients from each hospital. All baseline and clinical characteristics were collected by the research nurses.

Cost savings

Following the MRC guidelines, a sample size calculation for an evaluation study would be part of phase two. However, the PREDOCS programme is a newly developed, complex intervention targeting multiple adverse outcomes, and at this time, nothing is known about the likely range of the effect size, making a decision on the effect size premature.[33,34] Furthermore, in offering a multi-component intervention targeting multifactorial geriatric syndromes in a heterogeneous population (with respect to frailty) of older patients, a slight change in population features will influence the effect.[35] Additionally, hospitals are facing an increase in costs due to an increase in postoperative complications in these patients. Therefore, we decided to calculate theoretical cost savings of the PREDOCS programme in addition to the feasibility testing. We estimated potential cost savings, which can be achieved by implementing and executing the PREDOCS programme. Theoretical cost savings can be estimated by subtracting estimated costs from the estimated revenues.[20,36]

Analysis and reporting

We followed the recently proposed CReDECI reporting criteria concerning the feasibility of the intervention, including information on pilot-testing and presentation of all relevant results and their impact on the modelling of the final intervention.[37]

RESULTS

Between March and July 2012, 205 patients were screened for eligibility. Of those, 91 (44%) patients were excluded because of a limited number of study places, inability to visit the preoperative screening programme, or current hospitalisation. A total of 114 patients provided consent. After informed consent was given, 42 (20%) patients did not receive the intervention because they later declined participation or felt another consultation during the preoperative screening was too tiresome. A total of 72 patients received the intervention. Due to postponing surgery, two patients were excluded from the analysis. Therefore, the analysis was performed on a population of 70 patients. Figure 2 shows the flow of the recruitment and participation of the patients.

Testing procedures

Baseline and clinical characteristics of the 70 included patients are presented in Table 1. As patients received the PREDOCS programme in addition to usual care, they were equally satisfied of both the usual care and the PREDOCS programme (see Table 2). Patients and relatives appreciated the advice given in the PREDOCS programme and believed it was more in-depth than usual preparation. A patient stated: “It has been good. The nurse explained it very well, and I came to know exactly what will be done with me

and what I can do". Another patient stated: "I was very nervous before the surgery. The nurse explained it very well and really set me at rest".

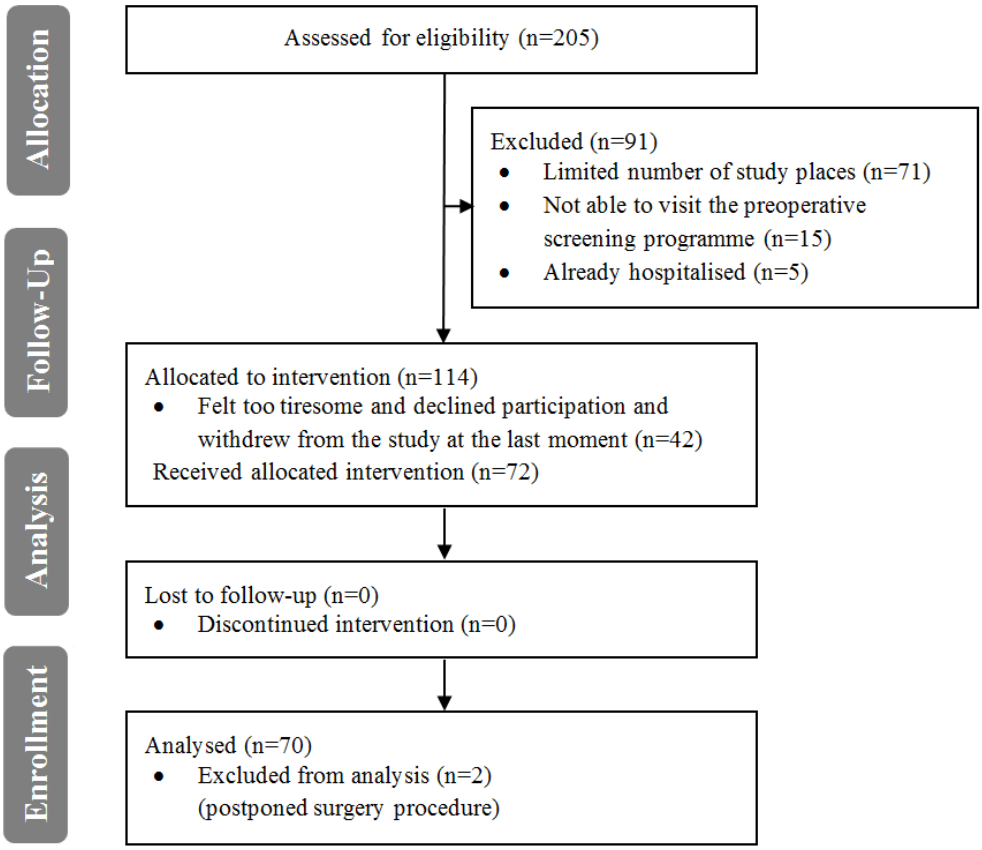

Figure 2 *Flowchart of the recruitment and participation*

After the four-hour training, the nurses felt competent to conduct the PREDOCS programme and thought the programme was complementary to usual care. They experienced that patients appreciated receiving useful information. One of the nurses stated the following: "You can see from the patients that they understand the information for the surgery much better now". Another nurse stated that "The PREDOCS programme is very much appreciated by patients. I did not observe any doubt by any patient".

Table 1 Baseline characteristics	
CHARACTERISTICS	N (%)
General	
Number of patients	70
Age (median, IQR)	74 (70-77)
Female gender (n, %)	21 (30)
BMI, kg/m^2 (median, IQR)	28 (25-30)
Surgical procedure (n, %)	
CABG	29 (41,4)
Valve	32 (45.7)
Combined CABG and Valve	9 (12.9)
Chronic Diseases (n, %)	
Diabetes	15 (21.4)
Renal failure	5 (7.1)
Liver failure	1 (1.4)
Thyroid disease	1 (1.4)
Hypertension	32 (45.7)
Extra Cardiac Vascular Pathology	10 (14.3)
COPD	11 (15.7)
Neurologic dysfunction	4 (5.7)
History of CVA / TIA	12 (17.1)
Stomach problems	8 (11.4)
Resources (n, %)	
Glasses	67 (95.7)
Hearing aids	13 (18.6)
Walking stick or walker	5 (7.1)
Wheelchair	1 (1.4)
Educational level (n, %)	
Lower vocational	26 (37.1)
Intermediate vocational	24 (34.3)
Higher vocational / University	20 (28.6)
Social status (n, %)	
Single / Widowed	20 (28.6)
Married / Domestic partnership	50 (71.4)
Handicap (n, %)	
Deaf / Deafness	14 (20)
Blind	1 (1.4)
Physically limited	5 (7.1)

BMI = Body Mass Index (kg/m2), CABG = Coronary Artery Bypass Graft, COPD = Chronic Obstructive Pulmonary Disease, CVA = Cerebrovascular Accident, TIA = Transient Ischaemic Attack

Nurses also experienced that adding the PREDOCS programme to the preoperative screening, in which the patient consulted with other healthcare professionals, was too tiresome for many patients. A nurse stated that "It is very busy for patients; they have many appointments in one day. Because it is for a research purpose, they are free to drop the nursing consult". Another nurse stated the following: "If patients decline participation in the study, it is almost always because of a very busy preoperative screening program".

Table 2 Patient satisfaction ratings for the usual care and the PREDOCS Programme*

	CLINIC 1	CLINIC 2	CLINIC 3	TOTAL
Number of patients	28	30	12	70
Satisfaction response: number (%)	25 (89)	19 (63)	10 (83)	54 (77)
Patient satisfaction, mean (sd)				
General prep. for surg. (usual care)	7.4 (6.3-8.6)	7.5 (6.5-8.6)	7.7 (6.2-9.2)	7.5 (6.4-8.7)
Pre-admission screening (usual care)	7.9 (7.1-8.6)	7.6 (6.0-9.2)	7.2 (5.9-8.5)	7.6 (6.4-8.9)
Intervention: PREDOCS programme	7.7 (6.9-8.5)	7.6 (6.3-8.9)	7.5 (6.6-8.4)	7.6 (6.6-8.6)
Time between POS† and Surgery				
Number of days (median, IQR)	16 (11-25)	28 (16-42)	13 (11-26)	19 (14.36)

sd = standard deviation, POS = Preoperative Screening, IQR = Interquartile Range

*) Assessed by a phone call within approximately seven days after discharge. Six questions were based on satisfaction, defined as the degree of meeting realistic expectations[27-29].

† Preoperative screening, four to two weeks before admission to the hospital.

Managers found that the PREDOCS programme was the missing link in equipping the nurses to prepare older patients for a hospital admission to undergo cardiac surgery. One manager stated the following: "If you look at risk factors for postoperative complications, it is eminently a nursing task to prevent this. Nurses are now provided with tools".

Managers indicated that the preoperative screening programme was performed during the period before the actual admission to the hospital, and many involved professionals have their consults with patients during the preoperative screening programme. One manager stated the following: "The patient visits the surgeon, the cardiologist, the assistant doctor, the physical therapist and the anaesthesiologist. And then, also the nurse starts a consultation". Another manager stated that "We also have patients from other hospitals, which complicates implementing the PREDOCS programme in an already complex schedule".

Moreover, nurses and managers noted two points for improvement. First, nurses attempted to explain the relationship between predictors and possible outcomes to patients, and patients found this concept difficult to understand because they tried to understand it in terms of direct causality. Second, the EuroSCORE was a predictor in three of the four prediction models that are part of the PREDOCS programme. Because the data for calculating this score for some of the patients were only collected during the hospital admission, the result of this score was not available for every patient before admission.

Estimating recruitment and retention

Of those patients who actually started the intervention, all completed the nursing consult. The mean time between receiving the PREDOCS programme and the cardiac surgery was 19 days, with a minimum of three days and a maximum of 81 days. Patients who had a short time prior to the hospital admission felt that they did not have enough time to transition to a good nutritional state. Most of these patients asked for detailed nutrition recommendations to be added to the general information.

Cost savings

In estimating potential cost savings, we looked at the costs of performing the PREDOCS programme and the costs of postoperative complications. The PREDOCS programme is executed by a nurse, and a PREDOCS consult takes twenty minutes to one hour, depending on the number of postoperative risks of the patient. A nurse is able to perform at least 1,000 PREDOCS consults per year, and the cost of a cardiac surgery nurse, including facilities, is an estimated 80,000 USD per year.[38,39]

In a study by Vonlanthen and colleagues[36] of 1,200 Swiss patients, the mean costs of major liver, pancreas, gastric bypass and colorectal surgeries in patients with complications increased by 51.5% (from 27,946 to 42,338 USD) per patient. The additional cost was based on additional pharmacological treatment for complications such as delirium, depression and infections. In a study by Gelsomino and colleagues[20] of 1,640 octogenarians and 1,230 septuagenarians undergoing cardiac surgery in Italy, the authors found a significant increase in the rate of adverse events, including agitation and disorientation, pneumonia, atrial fibrillation and hospital length of stay in the octogenarian population, leading to an increase in mean hospital costs of 38.5% (from 13,749 USD for septuagenarians to 19,042 USD for octogenarians) per patient.

At an average increase in cost of 5,000 USD per patient with postoperative delirium, depression, pressure ulcers or infections, the PREDOCS programme would be cost-effective if postoperative complications were prevented in sixteen of 1,000 patients. If additional costs were 14,000 USD per patient, the PREDOCS programme would be cost-effective if complications were prevented in six patients.

DISCUSSION

Through a stepwise, mixed-methods procedure using 70 patients at three hospitals, we showed that the PREDOCS programme was acceptable and feasible for patients and nurses to use in clinical practice. All patients received the full intervention. However, there were constraints in recruitment. Due to the focus on the pre-admission period and the dense schedule of the preoperative screening program, even a temporary implementation of the PREDOCS programme in the existing hospital structure was complicated.

In reporting this feasibility study, we followed the two CReDECI reporting criteria concerning 1) information on pilot-testing and 2) the presentation of all relevant results and their impact on the modelling of the final intervention. With regard to the first criterion, we tested the PREDOCS programme's acceptability and practicability and subsequently reported the findings in detail. Regarding the second criterion, important lessons were learned in how to implement the programme. The results were comprehensively reported.

To appreciate the present results, some aspects need to be considered. The data to calculate the EuroSCORE were not always available before hospital admission, forcing nurses to use their clinical judgment to estimate if the risk in a particular patient was higher or lower than 20%. When implementing the PREDOCS programme, the surgeon needed to calculate the EuroSCORE for all patients 65 years and older at the time the decision for surgery was made.

Regarding the use of predictors, nurses were not well prepared in every case. Nurses have to understand that there is a difference between a causal relationship and an association in risk assessment. If this idea is unclear, nurses can confuse patients with their assessment. This point should be discussed in the preliminary training for preparing nurses to execute the PREDOCS programme.

Amongst the 70 patients, we observed a large variation in waiting time for hospital admission: 3-81 days with a median time of 19 days (interquartile range of 14-36 days). The waiting time was predominantly influenced by the balance between surgery capacity and number of patients needing cardiac surgery. In the context of the PREDOCS programme, we advised the surgeon to consider taking at least two weeks to prepare patients at risk of complications when scheduling surgery, so patients would have sufficient time to prepare for their hospital admission.

Based on the given information, most patients asked for detailed nutrition recommendations to be added to the general information. This information was particularly important for patients who had a shorter waiting time before hospital admission. Therefore, written nutrition recommendations will be added to the PREDOCS programme.

Finally, two additional points must be considered. First, due to the limited ability to organise a nursing consult for conducting the PREDOCS programme, the number of study

places was restricted and 71 eligible patients (35%) had to be excluded. Because this was based on chance, it is unlikely this barrier led to selection bias.

Second, 42 eligible patients (20%) declined to participate, most stating that they found the preoperative screening programme already too full. Because the PREDOCS consult was for research purposes, the patient was free to skip this consult. This is both a limitation and a study outcome and must be taken into account when generalising the results.

Several studies previously tested the feasibility of a preadmission intervention. A preadmission interactive computerised smoking cessation programme was found acceptable and feasible in routinely encouraging 56 surgical preadmission clinic patients to stop or reduce their smoking. Forty-nine patients (retention rate 88%) fulfilled the programme that was part of the clinical pathway, and they found no constraints in recruitment.[40] In another study, a preadmission telephone screening (in twelve patients) was compared with a clinic assessment for preparedness (37 patients) in 49 patients undergoing endoscopy. The preadmission telephone screening and the clinic assessment for preparedness formed a part of the clinical pathway, leading to 100% recruitment and retention.[41]

Faes and colleagues[42] tested a complex fall prevention intervention and concluded that the use of the revised MRC guidelines eliminated the risk of evaluating unfeasible interventions and using poor designs. The guidelines also maximise the chance of having a successful intervention and evaluation, but they did not calculate a sample size. In our feasibility test of the PREDOCS programme, we experienced that the revised MRC guidelines helped guide us through the first two steps of phase two. Because nothing is known about the likely range of the effect size of the new multi-component PREDOCS programme, we found a decision on the effect size premature.

During this study, the PREDOCS programme was not integrated into the clinical pathway. During the preoperative screening, in which the patient consulted with other healthcare professionals, the schedule was tight, and adding the preoperative screening programme was tiresome for patients. If a hospital organisation has limited resources, there is a potential role for home care or a community nurse.

The next step in the development of the intervention is obtaining a valid and accurate estimate of its effect in clinical practice. Given that it is highly unlikely that the PREDOCS programme will result in more harm than benefit, a large randomised (cluster) trial may not be the ideal study design. A more feasible and low-cost approach could be a 'monitored implementation'. In such an implementation study, the possible effect of a multi-component intervention can be derived from measuring a significant decrease in the incidence of the study outcomes at the index hospitals and comparing this to the frequency of complications at control hospitals. Finally, a 'stepped-wedge design[43] may combine the benefits of both approaches by allowing all interested hospitals an opportunity to implement the intervention.

Conclusion

We found that it was feasible for patients and nurses to prepare older patients for cardiac surgery in the period before hospital admission. Nurses considered the PREDOCS programme as the missing link in preparing older patients for a hospital admission, and patients were very satisfied. Theoretically, the PREDOCS programme would already be cost-effective if it could prevent postoperative delirium, depression, pressure ulcers or infections in six to sixteen of 1,000 patients.

Nonetheless, we faced limitations in fitting the intervention into the existing preoperative pathway. We suggest either building the PREDOCS consult into the preadmission pathway of older cardiac surgery patients (ideally two to four weeks before surgery) or, alternatively, delivery of the PREDOCS programme at the patient's home by a community nurse.

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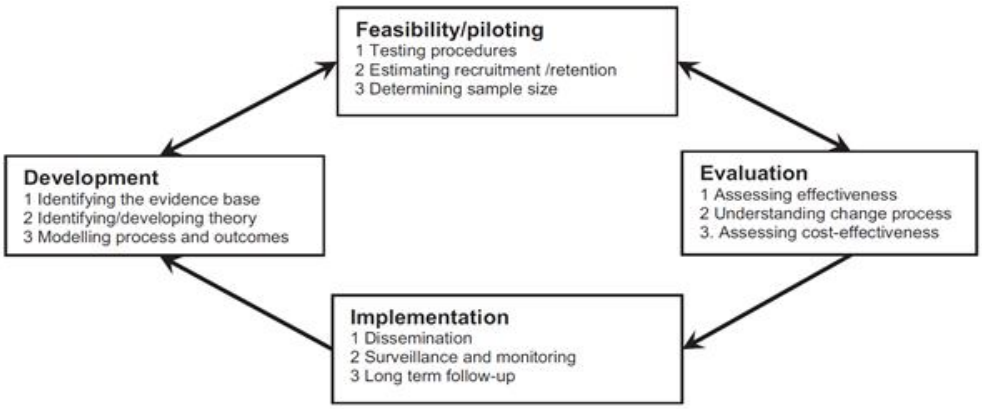
APPENDIX 1

The Medical Research Council guidelines of complex interventions

In fostering high quality intervention research, in 2000, the MRC developed a guideline based on the linear sequenced phases of drug development for use in the design, evaluation, and implementation of complex interventions[44]. In 2008, a revised version was published in which the process of developing and evaluating complex interventions was described according to cyclical phases to lead researchers through the process of designing and testing complex therapeutic interventions[23,24].



Key elements of the development and evaluation process of complex interventions, revised version 2008

APPENDIX 2

Patient satisfaction questionnaire for structuring the telephone interviews with the patients

Satisfaction was defined as the degree of meeting realistic expectations [27-29]. Following this definition, three open-ended questions were asked focusing on the expectations about 1) the general preparation for the surgery, 2) usual care, and 3) the PREDOCS programme. Also, closed questions satisfaction rating on a 10-point scale was asked, with higher scores indicating higher levels of satisfaction.

1) What did you expect from the general preparation for surgery?

……
……
……

2) How do you rate the provided support to the general preparation for surgery?

1 2 3 4 5 6 7 8 9 10

3) What did you expect from the usual care during the pre-admission screening?

……
……
……

4) How do you rate the provided support during the pre-admission screening?

1 2 3 4 5 6 7 8 9 10

5) What did you expect from consultation with the nurse (the PREDOCS intervention)?

……
……
……

6) How do you rate the provided support from the nurse during the consultation?

1 2 3 4 5 6 7 8 9 10

APPENDIX 3

Topic list for interviewing the manager

General information

- Job description and responsibilities
- Experience

Managers - Experiences with the implementation of the intervention

- What are your experiences with the implementation of the intervention in the organization?
- What went well?
- What went less well?
- Which problems did you have while performing the intervention within the organization?
- How did you solve these problems?
- Was it possible to prevent these problems? How?
- Do you have any suggestions for improvement?
- Are you planning to implement the intervention in the near future?
- What is the feasibility of this?

APPENDIX 4

Topic list for interviewing the research nurse

General information

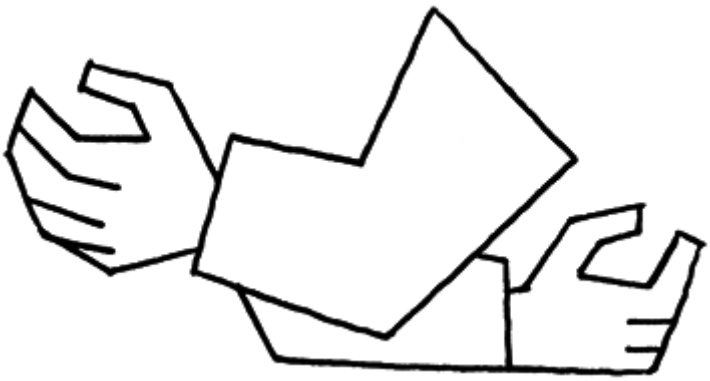
- Job description and responsibilities
- Experience

Experiences with implementing intervention

- What are your experiences with conducting the intervention in daily practice?
- Did you feel competent in conducting the intervention? Why?
- What went well?
- What went less well?
  How did you address any possible problems?
- What aspects of the intervention did appreciated? Why?
- Which aspects did you miss in the intervention?
- What aspects of the intervention could be improved?
  What was the average duration of preoperative screening program? How much time was spent on the intervention? (time in minutes)
  To what extent was this too short / enough / too long? Why?
  Was the intervention complementary to usual care? Why?
- Do you think that conducting the intervention is feasible for the nurses in the department / the ward?

Discussion

Predicting and preventing postoperative decline in older cardiac surgery patients



DISCUSSION

Delirium, depression, pressure ulcers and infection are frequently occurring postoperative complications in older cardiac surgery patients. Despite efforts to reduce their occurrence during hospitalization, their risk is still increasing.[1-9] Prevention of postoperative complications in cardiac surgery is mainly focused on the period of the hospital admission itself.[2-11] There is however a window of opportunity for preventive action before the hospital admission, as over 95% of the older cardiac surgery patients is scheduled for elective surgery.[12]

Improving patients' health condition in the preadmission period, aiming at decreasing the risk of postoperative complications, is one of the fundamentals of nursing care.[13,14] Therefore, this thesis focus on preventive nursing care targeting frequently occurring postoperative complications in older cardiac surgery patients already in the preadmission period.

The aim of this thesis is twofold:

1. To identify in the preadmission period older cardiac surgery patients at risk for postoperative delirium, depression, pressure ulcers or infection.
2. To provide nurses with an intervention for preparing these older patients before their hospital admission to prevent postoperative delirium, depression, pressure ulcers or infection.

Main findings

- Among twelve other models, two widely implemented models (Parsonnet, EuroSCORE) are superior in identifying patients with prolonged ICU length of stay in a patient population of all ages. (Chapter 1).
- However, the Parsonnet and the EuroSCORE models have relatively low discrimination and calibration in older patients. Consequently, both models should be applied with great care in the older cardiac surgery population, (Chapter 2).
- Patients appear to be predominantly at risk for only one specific postoperative complication. In this population, these risks can be best predicted separately. We identified sixteen preadmission patient characteristics with a predictive value for either postoperative delirium or depression or pressure ulcers or infection (Chapter 3).
- In systematically reviewing the literature we found that in preadmission prevention of postoperative complications, multi-component approaches are most effective in the prevention of postoperative depression and infection. High quality studies are urgently needed to evaluate preadmission preventive strategies to reduce postoperative delirium or pressure ulcers in older elective cardiac surgery patients (Chapter 4).

- Following the MRC guidelines, we developed the multi component 'PREDOCS' programme, which is to be applied two to four weeks before admission to the hospital. In this programme the nurse assesses the risk of postoperative complications in older cardiac surgical patients and provides tailor made interventions (Chapter 5).
- The PREDOCS programme was tested in clinical practice and appears to be feasible. However, it should be well integrated into the cardiac surgery clinical pathway. Alternatively, one might consider applying the programme in a home care setting (Chapter 6).

In this thesis we studied prediction models for identifying older cardiac surgery patients at risk for postoperative delirium, depression, pressure ulcers or infection. This thesis also presents a newly developed nursing intervention to prepare these older patients for their hospital admission with cardiac surgery. This so called PREDOCS programme appeared to be feasible for patients and for nurses in clinical practice. Although there is evidence for an effect of the separate components, the effects of PREDOCS programme in actually reducing the incidence of the four postoperative complications has not yet been tested.

The studies in this thesis are built on various methods from different research disciplines; prediction research (part 1 of this thesis) and intervention development research (part 2). Before further recommendations can be made based on the main findings, some reflections will be made regarding the two parts of the thesis.

Reflections on the development of the prediction models

In prediction research it has been advocated to first validate, and if necessary update, existing prediction models before developing new prediction models.[15] In the literature no models were available which explicitly predict postoperative complications in older cardiac surgery patients based on information available in the preadmission period. Therefore, as a proxy for a complicated operative and postoperative course, we validated existing prediction models for mortality and prolonged length of intensive care unit stay, which are developed in predominantly younger surgical patients (Chapter 1). Our study showed that these models have a poor performance in older patients. This is probably due to the large heterogeneity, e.g. comorbidities, among older patients (Chapter 2). Our findings are supported in the literature by the range of incidences of postoperative adverse events in the older population, reflecting most probably very heterogeneous populations and hence most likely explain the moderate results in the performance of these models.[16-19]

Subsequently, we aimed to identify risk factors for each of the four above mentioned postoperative outcomes separately. Unfortunately, these four new models were also limited in their discriminative ability in our older population. Although the discrimination was moderate, they showed good calibration and so were reasonably able to identify patients at increased risk for either delirium or depression or pressure ulcers or infection in the postoperative period, and could be used to support clinical decision making in the individual patient (Chapter 3). As such, the models were incorporated within our PREDOCS programme, aiding the nurse in identifying patients who could benefit from extra preventive interventions, which were further studied in part 2 of this thesis.

Reflections on development and feasibility testing of the intervention

In developing the PREDOCS programme, using a mixed methods research design[20], we followed the revised MRC guideline.[21] For the PREDOCS programme, we completed the first two phases concerning 1. development; 2. feasibility or piloting. In general the MRC guidelines worked properly for development of the PREDOCS programme. However, in the first phase we encountered two issues where we needed to conduct additional steps.

First, we encountered that the mechanisms of action of the intervention are not necessarily revealed. Therefore, on a non-formal base we used the framework of Van Meijel and colleagues in which building blocks are described for simultaneously developing and testing a complex nursing intervention in which the experience of the patient plays an important role.[22] After a thorough problem definition, the four building blocks: literature review, problem analysis, needs analysis and current practice analysis, were completed. Also, the framework provides guidelines for the actual development of the components of the intervention and the rationale for designing the complex intervention. This elucidates assumed mechanisms of action of predisposing and precipitating factors, which is an important step in the validation of the intervention. In this way, for every component, and the interplay between the components, the best achievable effect can be identified. In general the use of the MRC model helps to prevent the execution of time-consuming costly trials on poorly designed interventions.

Second, in completing the first phase of intervention development of the MRC guideline, we experienced at several stages in developing the PREDOCS programme indications to change medication prescriptions arose, and changing medication is not part of nurses' competencies and responsibilities in the Netherlands. Therefore, in a first round we consulted national experts in different relevant research fields and in a second round we consulted clinicians with an open question to evaluate the content of the intervention at that stage. Results from both rounds were discussed in two sessions with cardiac surgery nurses working in clinical practice (chapter 5). This way, in our opinion, we did not miss the opportunity to incorporate relevant tacit knowledge which cannot be identified from standard resources.

Following the second phase of the MRC guidelines in a mixed methods research design we tested the feasibility of the PREDOCS programme.[21] In preparing this study, we experienced that in the review process of the study protocol the ethical review board applied criteria for a randomized clinical trial, resulting for instance in a request for randomization. This generated discussion and delayed the start of the feasibility study. A feasibility study and a randomized clinical trial have different goals and use different methodology.[21] In our feasibility study, given the aim to study the change in practice we did not include a comparison group of patients who received usual care. As the field of care research is emerging, methodological procedures need to be further elaborated and shared with those responsible for consent.

Due to the sometimes short waiting time between indication for surgery and the surgery itself – in some patients only 3 days – it was not always meaningful and possible to measure the experiences of patients with the PREDOCS programme. Because it was unclear how many patients would experience a very short waiting time, we decided not to measure the experiences before admission and limit ourselves to measure the satisfaction of the patient at the end of the admission.

Recommendations for further research

The moderate results in the performance of prediction models in older cardiac surgery patients are most likely explained by the heterogeneity with respect to frailty in these older patients. Frailty is related to many common and comorbid health problems and is multifactorial in etiology.[18,23,24] Therefore, in research with the aim to develop an effective prediction model for older patients, this multifactorial origin should be properly addressed, preferably by developing specific models for predicting specific adverse outcomes, specifically in the older population.

Although, we carefully developed the PREDOCS programme following the extended stepwise multi-method of the revised MRC-guidelines (Chapter 5) and estimated that its use is already cost effective when only 0.6% to 1.6% of the patients would benefit (Chapter 6), it makes sense to test the effect of the PREDOCS programme. An adequate approach with relative low costs for measuring the effect of the PREDOCS programme would be a monitored implementation trial, for example in a study with a 'stepped wedge' design.[25] Such a design is particularly relevant in cases where the intervention will likely do more good than harm. In a stepped wedge design study an intervention is sequentially rolled-out over a number of time periods were the order in which departments implement the intervention is determined at random. In such a study with a complex design, careful planning and monitoring are required in order to ensure that a robust evaluation of the effectiveness of the intervention is undertaken.[25,26]

The concept of a better preparation of older patients before hospital admission is not limited to cardiac surgery only. Also in other major surgery areas, such as orthopaedic surgery, abdominal surgery and cancer surgery, improvements in surgery techniques make it now possible to operate on frail older patients.[27-33] But, similar to the domain of cardiac surgery, the question arises "how to prepare a patient for the hospital admission to decrease the risk on a postoperative complication?". This question can be addressed by developing programmes such as the PREDOCS programme in these surgical areas, by taking the development process of the PREDOCS programme as an example.

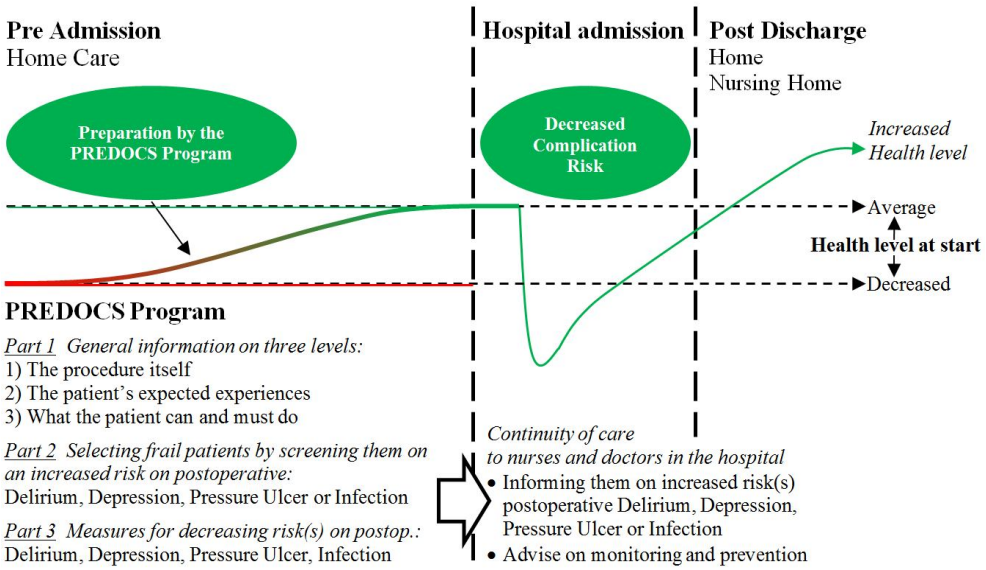


Figure 1 *Increased health level of a patient following the PREDOCS programme for safely passing the hospital admission with cardiac surgery. The upper dashed horizontal line represents the average health level of a patient before admission and the lower horizontal line represents the health level of a patient with decreased health level before admission*

Recommendations for clinical practice

The PREDOCS programme consists of a nursing consult which the patient receives two to four weeks before the surgical procedure. This consult consists of three phases (See figure 1):

- A generic preparation for surgery in all patients,
- Identification of patients at risk for postoperative delirium, depression pressure ulcers or infection, and

- Informing patients with an increased risk for a specific complication on how to specifically prepare themselves to prevent this complication during the upcoming hospital admission.

The first generic part is for all older patients (both high and low-risk), and includes provision of the general information on three levels: 1) The procedure itself; 2) The patient's expected experiences, and 3) What the patient can and should do. This part includes also guidance on the importance of good nutrition, arranging the presence of steady social support, and the awareness of the importance of adequate postoperative pain management. Following this procedure, patients with an increased risk receive information on additional actions that will give them an opportunity to reduce their risk.
In the perspective of continuity of care when a patient is screened on an increased risk, the nursing department of the hospital will be informed with guidelines on extra care for this patient during hospitalization.

It should be considered to extend the clinical path of the hospital also to the preadmission period, by building the PREDOCS programme into the cardiac surgical pathway. An alternative could be to fit the PREDOCS programme into the home care process for older patients indicated and scheduled for cardiac surgery.

In clinical practice the time between the indication of the patient for cardiac surgery and the actual day of surgery does not only vary per patient and per hospital, but due to fluctuations in demand and supply, it also varies over time. As a consequence, when applying the PREDOCS programme in clinical practice, not all patients will have at least two weeks of preparation time. Provided that the intervention will prove to be effective in reducing the incidence of these postoperative complications and when medically acceptable, taking at least two weeks preparation time for the patient at risk should be considered when scheduling the patient for cardiac surgery.

When implementing the PREDOCS programme in clinical practice, patients should be continuously screened for an increased risk of complications in the postoperative period. In a study in 250 nurses (chapter 5) we found that the majority of the nurses responded that they underestimate the incidence of delirium, depression, and pressure ulcers in their department, yet they do not screen routinely for these conditions. A negative self-sustaining situation emerged: because they do not screen routinely they underestimate the incidence in the postoperative period and so miss the sense of urgency that an older patient should be prepared for a hospital admission with cardiac surgery. Therefore, in order to be able to improve the nursing care in clinical practice, we highly recommend screening older cardiac surgery patients on an increased risk of delirium, depression, pressure ulcers and infection during the complete admission period. This will enable the opportunity to implement interventions such as the PREDOCS programme.

Recommendations for education

Older patients should be adequately prepared before an elective hospital admission. Despite the fact that this is in accordance with the fundamentals of nursing[13,14], this notion is unfortunately not common in nursing practice.[1-9] Consequently, when implementing a programme such as the PREDOCS programme in clinical practice, it should at the meantime be included in nursing educational curricula. This enables nurses and future nurses to become aware of the fact that older patients should be prepared for a hospital admission. Moreover, they learn how to prepare these older cardiac surgery patients for a hospital admission.

At this moment we face an increase of older and more frail people admitted to hospitals.[1, 23,27-35] Most nurses are not aware of the fact that current nursing knowledge is based on eras when the share of older people was much smaller or even not present (chapter 4). They are unaware of the dangers of hospitalization for older cardiac surgical patients[2-9] This fact is not only true for cardiac surgery patients, but also for patients in other major surgery areas.[27-33] Also nursing students are not aware of the fact that older patients should be prepared for a hospital admission.[36] From the perspective of education, knowledge about this notion should be trained both to nurses working in clinical practice and to future nurses following a study to become a nurse.

In implementing the PREDOCS programme, it has to be decided where it will be implemented. In case the hospital decides on extending the clinical path of cardiac surgery for older people to the preadmission period (backward integration), cardiac surgery nurses in the hospital should be trained in performing the PREDOCS programme. In case the home care organization decides to prepare older cardiac surgery patients as an extension to the hospital clinical path (forward integration), a specialized home care nurse needs be trained. This training can be done in a session of four hours and is preferably repeated annually. The training includes an introduction to the PREDOCS programme, a physiotherapist practicing how to instruct patients in doing breathing exercises, and improvement of application of the PREDOCS programme into the hospital or home care organization structure.

Not only nurses who execute the PREDOCS programme have to be aware of the fact that preadmission preparation is expected to have a tempering effect on the incidence of postoperative complications, also indirectly involved nurses have to be made aware of this. Therefore, we developed a four minute instructional video, which can be seen at:
http://www.youtube.com/watch?v=le6ihjd-DAI
Although this video can be seen individually, we advise to watch it with the nursing team and discuss afterwards how it is experienced and what can be remembered.

Conclusion

With the growing proportion of older people in cardiac surgery, nurses have a crucial role in supporting older patients to optimally prepare themselves for a hospital admission. The PREDOCS programme allows nurses to take the lead in supporting older patients to prepare themselves in the preadmission period, with the aim to safely pass the hospitalization without experiencing a postoperative delirium, depression, pressure ulcer or infection.

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GLOSSARY

Delirium

A delirium is diagnosed as a disturbance of consciousness with reduced ability to focus, sustain or shift attention. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by a medical condition, substance intoxication, or medication side effect.[1]

In chapter 3 of this thesis, delirium was measured using the Delirium Observation Screening Scale. This scale was validated against the above described diagnosis.[2]

Depression

A depression or Major Depressive Disorder (MDD) is diagnosed as[1]:

A. At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either a depressed mood or loss of interest or pleasure.
    1. Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
    2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation made by others)
    3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
    4. Insomnia or hypersomnia nearly every day
    5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
    6. Fatigue or loss of energy nearly every day
    7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
    8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
    9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

B. The symptoms do not meet criteria for a mixed episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

The mean length of postoperative stay in the hospital for cardiac surgery patients is seven to ten days and the minimal length of time necessary to diagnose a postoperative depression using these criteria cannot be achieved. Therefore, in chapter 3 of this thesis, depression was measured using the Geriatric Depression Screening Scale.[3]

Frailty

A clinical syndrome in which three or more of the following criteria are present in community dwelling older people[4]:

A. Unintentional weight loss (10 lbs/4.5 kg in the past year)
B. Self-reported exhaustion
C. Weakness (grips strength)
D. Slow walking speed
E. Low physical activity

Nosocomial infection (hospital acquired infection)

An infection acquired in hospital by a patient who was admitted for a reason other than that infection. An infection occurring in a patient in a hospital or other health care facility in whom the infection was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge, and also occupational infections among staff of the facility.[5]

Pressure Ulcer (Decubitus)

Pressure ulcers are localized injury to the skin and/or underlying tissue usually over a bony prominence (e.g., the sacrum, trochanter, ischium, or heel), as a result of pressure, or pressure in combination with shear and/or friction.[6,7]

Older

65 years and older

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SUMMARY

The proportion of older people in the western population is rapidly growing, and improvements in cardiac surgical techniques and anaesthetic procedures allow surgery even in frail patients. This has the advantage that increasingly older, sicker, and higher-risk patients can undergo cardiac surgery without facing a high mortality risk. However, if these older patients experience postoperative complications, they do not benefit from the surgery. Delirium, depression, pressure ulcers and infections are frequent complications in the postoperative period in older cardiac surgery patients. These complications hamper recovery and are associated with functional and cognitive decline and a decreased quality of life after discharge. Often, this decline has already started before hospital admission. These patients enter the hospital with a below-average health condition, which increases their risk of complications. Therefore, care of older cardiac surgery patients, particularly those who are vulnerable should not be limited to the time spent in the hospital, but the preadmission period should be used to optimize the patient's condition.

This thesis investigates a preparation program, delivered by the nurse, for older patients undergoing cardiac surgery. The first part (chapters one to three) focuses on the selection of older patients at risk of postoperative complications. The second part (chapters four to six) describes the development of a preparation programme for older cardiac surgery patients..

To enable the nurses to determine a patient's risk of experiencing postoperative complications, we first focused on the risks directly after surgery. ***Chapter 1*** describes a systematic review of models predicting a prolonged intensive care unit stay, which were used as a proxy for surgical and intensive care unit complications. We identified twenty models, of which we then applied fourteen to a large dataset that included patients of all ages. Of the three models that performed the best, two are widely implemented in clinical practice (Parsonnet, EuroSCORE), although they were originally designed for the prediction of mortality.

These models that were identified have the disadvantage that they were developed in the general population in the eighties and nineties, when the share of older people undergoing cardiac surgery was smaller than today. As a consequence, it was unclear how these models would perform in older patients. Therefore, in ***Chapter 2***, we quantified the performance of the three prediction models in different age groups. With increasing age, we found a decrease in performance of the models and in particular an increase in variation of predicted risks, suggesting an increase in heterogeneity with respect to frailty. Therefore, risk prediction for a prolonged intensive care unit stay after cardiac surgery using these existing models should be performed with great care in older patients.

We then focused on the selection of older patients with an increased risk of postoperative delirium, depression, pressure ulcers or infections, based on information available two to four weeks before surgery (in the preadmission period). ***Chapter 3*** describes a study in which we developed models to predict the risk of postoperative delirium, depression, pressure ulcers and infections in older patients waiting to undergo cardiac surgery. We identified sixteen factors that were predictive for an increased risk of postoperative complications (use of fraxiparine or insoles, deafness, being physically disabled, living alone, being dependent on informal care, the logistic EuroSCORE, the serum creatinine level, and a history of tricuspid insufficiency, renal failure, CVA or TIA), most of which were clinical factors, and two of which related to the (psycho)social domain. If these predictors are known before admission, patients with increased risk can be selected accordingly for more intensive evaluation and preparation to reduce their risk.

Chapter 4 describes a systematic review of the literature on preadmission interventions designed to prevent postoperative complications. We found that multi-component approaches that include different single interventions have the strongest effect in preventing postoperative depression, pulmonary complications and prolonged stay at the intensive care unit and in hospital. We also suggested that high-quality studies are urgently needed to evaluate preventive strategies to reduce postoperative delirium or pressure ulcers in older patients elected for cardiac surgery. These results formed a base for developing a preventive intervention.

Chapter 5 describes the development of an evidence-based multi-component nursing intervention using a mixed-methods design. This programme (PREDOCS programme) is to be used in the preadmission period to improve patients' physical and psychosocial conditions to reduce their risk of postoperative complications. We developed the PREDOCS programme according to the guidelines of the Medical Research Council on the development of a complex intervention, as is described in detail in this chapter. The intervention consists of a consult by a nurse two to four weeks before surgery and comprises of three parts: a general part for all patients, identification of patients at increased risk, and education of the selected patients on how to reduce their risk before hospital admission. The content of the PREDOCS programme is described in a four-minute instructional video, available at

http://www.youtube.com/watch?v=le6ihjd-DAI (English version)
http://www.youtube.com/watch?v=UiSBNmSkwcQ (Dutch version)

In ***chapter 6***, we tested the feasibility of the PREDOCS programme used by nurses in the preadmission period in a heterogeneous population of 70 older cardiac surgery patients at three hospitals in the Netherlands. In a mixed-methods multicentre study according to the Medical Research Council guidelines we investigated feasibility of the programme and calculated the theoretical cost effectiveness based on the study results. Patients were

equally satisfied with the usual care and the PREDOCS programme. The involved nurses were satisfied with the tools for guiding patients to reduce their risk of postoperative complications and thought the PREDOCS programme was complementary to usual care. Both patients and nurses felt that the preoperative screening, in which the patient consulted with other healthcare professionals, was tiresome for the patient. Implementation of the programme in the existing hospital structure appeared to be difficult. Therefore, the PREDOCS programme should be built into the hospital clinical pathway or performed at home. Based on our theoretical calculations, the PREDOCS programme turned out to be cost-effective, with only six to sixteen of 1,000 patients prevented from experiencing these postoperative complications.

The need for preparation of older patients undergoing surgery is not restricted to the domain of cardiac surgery. In other major types of surgery, such as orthopaedic, abdominal and cancer surgery, improvements in surgery techniques have made it possible to operate on frail older patients. Similar prediction models can be developed for other types of surgery, and interventions such as the PREDOCS programme can be used, or developed using a development process similar to the one for the PREDOCS programme described in this thesis.

Improving patient outcomes is not achieved by merely implementing programmes such as the PREDOCS programme into clinical practice. Most nurses are not aware that current nursing knowledge is based on research that was not performed on older people and that was conducted in eras when the elderly population was much smaller. Therefore, the use of such prevention programmes, and more importantly the awareness that older patients should be prepared before hospital admission, should be implemented in nursing educational curricula as well.

With a growing proportion of older people undergoing cardiac surgery, nurses play a crucial role in optimising older patients' preparation for hospital admission. The PREDOCS programme allows nurses to take the lead in supporting older patients to prepare themselves in the preadmission period and aims to prevent postoperative delirium, depression, pressure ulcers and infections.

SAMENVATTING

Het aandeel ouderen in de westerse bevolking groeit snel en verbeteringen in cardio chirurgische technieken en anesthesiologische procedures maken het zelfs voor zwakke patiënten mogelijk om een openhartoperatie te kunnen ondergaan. Dit heeft het voordeel dat steeds oudere, ziekere en hoger risico patiënten een openhartoperatie kunnen ondergaan, zonder dat zij een hoog risico lopen om te overlijden. Helaas krijgen veel van deze oudere, meer kwetsbare, patiënten complicaties als delirium (tijdelijke verwardheid), depressie, decubitus (doorligwonden) en infecties na de operatie, waardoor zij niet of nauwelijks van de operatie profiteren. Oudere patiënten die een of meer van deze postoperatieve complicaties hebben opgelopen krijgen vaker te maken met functionele en cognitieve achteruitgang en een verminderde kwaliteit van leven na ontslag uit het ziekenhuis dan patiënten die geen complicatie na de operatie hebben opgelopen. Het hebben van een of meer van deze complicaties leidt tot een lager gezondheidsniveau en belemmert ook het herstel na de operatie. Een dergelijk verlaagd gezondheidsniveau van de patiënt is vaak al aanwezig voor de ziekenhuisopname en deze patiënten worden dan in het ziekenhuis opgenomen met een lager dan gemiddelde gezondheidstoestand, hetgeen hun risico op complicaties vergroot. Daarom moet bij de oudere kwetsbare openhartoperatiepatiënt de zorg niet worden beperkt tot de tijd in en na de ziekenhuisopname, maar moet de periode voor de ziekenhuisopname worden gebruikt om de patiënt te optimaliseren.

In dit proefschrift wordt de ontwikkeling beschreven van een verpleegkundig programma voor het voorbereiden van oudere patiënten op een ziekenhuisopname met een openhartoperatie. Het eerste deel (hoofdstukken 1, 2 en 3) is gericht op de selectie van die oudere patiënten die een verhoogd risico op een postoperatieve complicatie hebben. In het tweede deel van dit proefschrift (hoofdstukken 4, 5 en 6) wordt de ontwikkeling van het voorbereidingsprogramma voor oudere openhartpatiënten beschreven.

Om verpleegkundigen in staat te stellen het risico op postoperatieve complicaties van een patiënt te bepalen, zijn eerst de risico's geïnventariseerd die patiënten direct na de operatie lopen. ***Hoofdstuk 1*** beschrijft een systematische review van modellen die een verlengd verblijf op de intensive care voorspellen. Een langer verblijf op de intensive care kan worden gezien als een maat voor het optreden van complicaties tijdens of vlak na de operatie. Met de systematische review zijn twintig modellen geïdentificeerd, waarvan er veertien in een grote dataset van patiënten van alle leeftijden konden worden getest. Van de drie beste voorspellende modellen worden er twee op grote schaal in ziekenhuizen wereldwijd toegepast (Parsonnet, EuroSCORE).

Deze geïdentificeerde modellen zijn ontwikkeld in de jaren tachtig en negentig op basis van gegevens van patiënten van alle leeftijden. In die jaren was het aandeel oudere mensen die een openhartoperatie onderging veel kleiner dan nu het geval is. Het was daarom onduidelijk of deze modellen ook bij oudere patiënten een verlengde opnameduur op de intensive care konden voorspellen. Daarom zijn in ***hoofdstuk 2*** de prestaties van de drie voorspelmodellen in verschillende leeftijdsgroepen gekwantificeerd. Hieruit bleek dat hoe ouder de patiënten hoe minder de modellen in staat waren een goede voorspelling te doen. Deze afname van de voorspellende waarde van de modellen bij het toenemen van de leeftijd van patiënten wijst op een toename van heterogeniteit ten aanzien van kwetsbaarheid in deze patiënten. Daarom moet met het gebruik van deze modellen in de praktijk rekening worden gehouden met de beperkte voorspellende waarde bij oudere patiënten.

Daarna hebben we ons gericht op de selectie van oudere patiënten met een verhoogd risico op de meest voorkomende postoperatieve complicaties: delirium, depressie, decubitus of infectie, zoals beschreven in ***hoofdstuk 3***. Gebaseerd op patiëntgegevens die 2-4 weken voor de operatie beschikbaar zijn (in de preopname periode), hebben we modellen ontwikkeld waarmee het risico kan worden voorspeld op het oplopen van een postoperatieve delirium, depressie, decubitus of infectie. Zestien patiëntenkenmerken die voorspellend zijn voor een verhoogd risico op postoperatieve complicaties zijn geïdentificeerd, zoals het gebruik van fraxiparine, inlegzolen, doofheid, fysiek gehandicapt zijn, alleenstaand, afhankelijk zijn van informele zorg, de logistische EuroSCORE, serumcreatinine en het hebben gehad van een tricuspidalis klep insufficiëntie, nierfalen, CVA of TIA. De meeste van deze zestien patiëntenkenmerken zijn klinische factoren en slechts twee ervan bevinden zich in het psychosociale domein van functioneren. Als deze voorspellers bekend zijn vóór de opname in het ziekenhuis, dan kunnen patiënten met een verhoogd risico worden geselecteerd voor een intensieve evaluatie en voorbereiding om hun risico te verminderen.

Hoofdstuk 4 beschrijft een systematische review van de literatuur over preopname interventies om postoperatieve complicaties te voorkomen. We vonden dat multi-component benaderingen die meerdere enkelvoudige interventies omvatten het meest effectief zijn in het voorkomen van postoperatieve depressie, pulmonale complicaties en langdurige verblijf op de intensive care en in het ziekenhuis. We constateerden dat studies van hoge kwaliteit nodig zijn die effecten laten zien van strategieën om postoperatief optredende delirium of decubitus bij oudere openhartoperatie patiënten te voorkomen. De resultaten van deze systematische reviewstudie vormden een basis voor het ontwikkelen van een preventieve interventie.

Hoofdstuk 5 beschrijft de ontwikkeling van een evidence-based multi-component verpleegkundige interventie met behulp van een zogenaamd ‘mixed-methods’

onderzoeksontwerp. Dit programma (PREDOCS programma) kan worden gebruikt in de preopname periode. Met het programma kan de patiënt 2-4 weken voor de ziekenhuisopname zijn of haar fysieke en psychosociale omstandigheden verbeteren om het risico op postoperatieve complicaties te verminderen. Het PREDOCS programma is ontwikkeld volgens de richtlijnen van de Medical Research Council voor het ontwikkeling van een complexe interventie. Het programma bestaat uit een consult door een verpleegkundige 2-4 weken voor de operatie en omvat drie delen: een algemeen deel voor alle patiënten, de identificatie van patiënten met een verhoogd risico en het instrueren van de geselecteerde patiënten over hoe ze hun risico kunnen verminderen vóór de ziekenhuisopname. De inhoud van het PREDOCS programma wordt in een vier minuten durende instructie video beschreven, welke via de onderstaande link is te vinden:

http://www.youtube.com/watch?v=UiSBNmSkwcQ (Nederlandse versie)
http://www.youtube.com/watch?v=le6ihjd-DAI (Engelse versie)

In ***hoofdstuk 6*** is het PREDOCS programma getoetst op haalbaarheid in een heterogene populatie van 70 oudere cardiochirurgische patiënten in drie ziekenhuizen in Nederland. Opnieuw volgens de richtlijnen van de Medical Research Council is in een 'mixed-methods' studie onderzocht of het programma haalbaar is voor verpleegkundigen en patiënten. Op basis van de resultaten is de theoretische kosteneffectiviteit berekend. De patiënten waren zowel tevreden met de gebruikelijke zorg als met het PREDOCS programma. De betrokken verpleegkundigen waren tevreden met de hulpmiddelen voor het begeleiden van patiënten om hun risico op postoperatieve complicaties te verminderen. Zij vonden het PREDOCS programma een aanvulling op de gebruikelijke zorg. Zowel patiënten als verpleegkundigen vonden dat de preoperatieve screening, waarbij de patiënt ook andere professionals consulteert, vermoeiend is voor de patiënt. Het inpassen van het programma in de bestaande ziekenhuis structuur bleek moeilijk te zijn. Het klinisch pad moet worden aangepast om het PREDOCS programma in te kunnen passen of het PREDOCS programma moet binnen de thuiszorg worden uitgevoerd. Op basis van onze theoretische berekening, blijkt het PREDOCS programma al rendabel te zijn als er bij slechts zes tot zestien van 1000 patiënten een postoperatieve complicatie wordt voorkomen.

De noodzaak van het voorbereiden van oudere patiënten op een ziekenhuisopname met een operatie blijft niet beperkt tot het gebied van hartchirurgie. In andere chirurgische gebieden, zoals orthopedische, abdominale en kankerchirurgie zijn verbeteringen in chirurgische technieken die het mogelijk hebben gemaakt om ook kwetsbare oudere patiënten te opereren. Voor patiënten die deze andere vormen van chirurgie moeten ondergaan kunnen op een vergelijkbare wijze voorspellende modellen worden ontwikkeld. Ook kunnen interventies, zoals het PREDOCS programma worden gebruikt of ontwikkeld met behulp van een ontwikkelingsproces dat vergelijkbaar is met die van het PREDOCS programma, zoals beschreven in dit proefschrift.

Het verbeteren van resultaten van zorg en behandeling voor patiënten wordt niet alleen bereikt door het implementeren van programma's zoals het PREDOCS programma. Veel verpleegkundigen zijn zich niet bewust van het feit dat de huidige verpleegkundige kennis is gebaseerd op onderzoek dat werd uitgevoerd in periodes waarin het aandeel ouderen in de algemene bevolking, en in de chirurgische populatie, veel kleiner was dan nu. Daarom moet het gebruik van dergelijke preventieprogramma's en het besef dat oudere patiënten moeten worden voorbereid voor een ziekenhuisopname, in de curricula van verpleegkundige lesprogramma's worden opgenomen.

Met het almaar toenemend aandeel ouderen dat openhartchirurgie ondergaat, spelen verpleegkundigen steeds meer een cruciale rol in het optimaliseren en voorbereiden van oudere patiënten voor een opname in het ziekenhuis. Met het PREDOCS programma kunnen verpleegkundigen het initiatief nemen in het ondersteunen van oudere patiënten zodat zij zich vooraf aan de ziekenhuisopname al kunnen voorbereiden om na de operatie de kans op een delirium, depressie, decubitus of infectie te verkleinen.

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Gezondheidswetenschap staat ten dienste van het steeds weer verder ontwikkelen van een state of art patiëntenzorg. Door de medewerking van patiënten aan onderzoek is onderzoek mogelijk. Voor de onderzoeken die beschreven staan in de eerste twee hoofdstukken van dit proefschrift maakten wij gebruik van gegevens van 11.395 patiënten in de Isala klinieken die daarvoor hun toestemming verleenden. Voor de onderzoeken in het derde en vijfde hoofdstuk hebben wij gebruik gemaakt van gegevens van 2.716 patiënten in de Isala klinieken die daarvoor niet alleen hun toestemming verleenden, maar ook bereid waren daar extra gegevens voor af te geven. In het onderzoek dat beschreven staat in hoofdstuk 6 hebben 70 patiënten in het Antonius ziekenhuis in Nieuwegein, de Isala Klinieken in Zwolle en het UMC Utrecht het PREDOCS programma uitgeprobeerd. Ook gaven negen patiënten in interviews ons een inkijkje in hoe oudere patiënten een ziekenhuisopname met een openhartoperatie ervaren. Graag dank ik alle 14.190 patiënten die bereid waren ons hun vertrouwen te geven en hun gegevens en ervaringen met ons te delen.

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CURRICULUM VITAE

Roelof was born on February 17, 1965, in Purmerend, The Netherlands. After finishing at the Geert Groote College ("Vrije School" or "Waldorf School") in Amsterdam in 1985, he started to study nursing at the University of Applied Sciences in Amsterdam and began to work as a care helper in the mentally disabled care. Some years later, he switched to private nursing care, and in 1989, he obtained his bachelor's degree in Nursing. He then travelled to West Africa, where he worked for half a year as a nurse at St. Patricks Hospital and in the surrounding rural area in central Ghana.

After his return, he worked as a nurse in several general hospitals in Amsterdam, and in 1990, he moved to Maastricht to study Nursing Science at the University of Maastricht. In addition, he worked as a nurse caring for chronic psychiatric patients at the psychiatric hospital Vijverdal, and in 1993, he gained his master's degree.

From 1993 to 2000, he worked at the Dutch Institute for Healthcare Improvement (CBO) as a quality facilitator in hospitals, trainer of quality facilitators in The Netherlands and Germany and project leader of several national nursing quality care projects. In 1997, he obtained his bachelor's degree in Marketing, and in 2000, as a quality manager, he started working at the rehabilitation centre Heliomare. In 2004, he obtained his qualification for teaching bachelor's and master's courses, and in 2006, Roelof was invited to start a PhD programme at the University of Utrecht. He studied Epidemiology at the University of Utrecht's Graduate School of Life Sciences, from which he received his master's degree in 2009.

Since 2006, he has been working at the University of Applied Sciences-Utrecht as a researcher for the chair of Nursing and Paramedical Care for people with chronic illnesses and as a lecturer at the Master Care Trajectory Design, Bachelor of Nursing and the Master of Advanced Nurse Practitioner programmes. Roelof is determined to continue research and education involving clinical practice in the nursing of older people.

PREDICTING AND PREVENTING POSTOPERATIVE DECLINE IN OLDER CARDIAC SURGERY PATIENTS ROELOF ETTEMA