DEVELOPMENT, IMPLEMENTATION, AND EVALUATION OF HIGH-RISK SURGERY RELATED CLINICAL PATHWAYS IN THE INTENSIVE CARE:

EFFECTS OF A PROCESS INTERVENTION

MARION VAN DER KOLK

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EFFECTS OF A PROCESS INTERVENTION

B.M. van der Kolk

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Promotoren:
Prof. dr. P. Pickkers
Prof. dr. C.J.H.M. van Laarhoven

Copromotor:
Dr. M. van den Boogaard

Manuscriptcommissie:
Prof. dr. G.P. Westert
Prof. dr. W.J. Morshuis
Prof. dr. P. Kabat (Wageningen University & Research)

Paranimfen
Shalini Soechitram
Bernadette Wieberdink -Wardenburg

The Pathway, like life, is not a competition
Never get seized by the wish to do too much
your body will soon demand an explanation
Look around, observe and taste.
That's what the Pathway will teach you

Via Francigena, Canterbury to Rome, Archbishop Siegeric A.D. 990

Table of contents

General Introduction
and outline of this thesis

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The landscape of peri-operative care in high-risk surgery is diverse, as many departments and care-providers have a role in the care for the patient during the peri-operative period. The definition of high-risk surgery has been the topic of perceptions, assumptions and many discussions for decades(1). High-risk surgery can be defined as a surgical procedure with an expected high mortality and high morbidity risk(2). In many patients an admission to an Intensive Care Unit (ICU) is needed as part of their treatment in the peri-operative period and following high-risk surgical interventions. As a consequence, variability in the quality of peri-operative care will have an influence on the clinical outcome of these patients(3, 4). This variability in outcome and recent improvements of outcome may be related to several factors, including more-up-to-date technology, a closed format intensive care organisation, numbers of nursing staff, education level of staff, use of guidelines and multidisciplinary team communication (5). As a result, the high-risk patients' journey through the hospital may encounter many hurdles, obstacles and slippery slopes or have smooth transitions between medical and nursing professionals and departments. Audits, ward-visits and in-depth analyses of complications, reveal that both journeys may exist alongside each other in one system. Differences between the perceived use of protocolized care, and the care patients actually receive during their hospital stay, are often unknown to patients, care givers and clinical leaders. For example in the field of sepsis, variability of care and the effect on outcome has been investigated in patients in the ICU(6). Better compliance with guidelines translates in better outcome of critically ill patients (7), and there is room for improvement (8), also in The Netherlands (9).

As mentioned, Work-as-Imagined (WAI), developed and built into guidelines, will not always mirror utilisation of these guidelines: Work-as-Done (WAD) (10). Because these differences will be the result of resources, integrated processes, care-providers and patient characteristics, they can all have an effect on the outcome of the patient(11). Fortunately, systems, team members and patients do often show resilience and the positive effect of this resilience can be that the clinical impact of variability in treatment may be limited. Nevertheless, these data indicate that improvements are clearly possible and likely, may result in better outcome for the ICU patient (12). As a consequence, a safe patients' journey through the hospital system needs processes where Work-as-Done will better represent the use of guidelines and variances underneath. This journey also has to rely on a certain amount of resilience within the system.

The total quality of care, provided for patients, is the product of many different procedures and systems connected together. According to Donabedian, quality of care can be divided in three domains: structure, process and outcome (5, 13). Each domain is character-

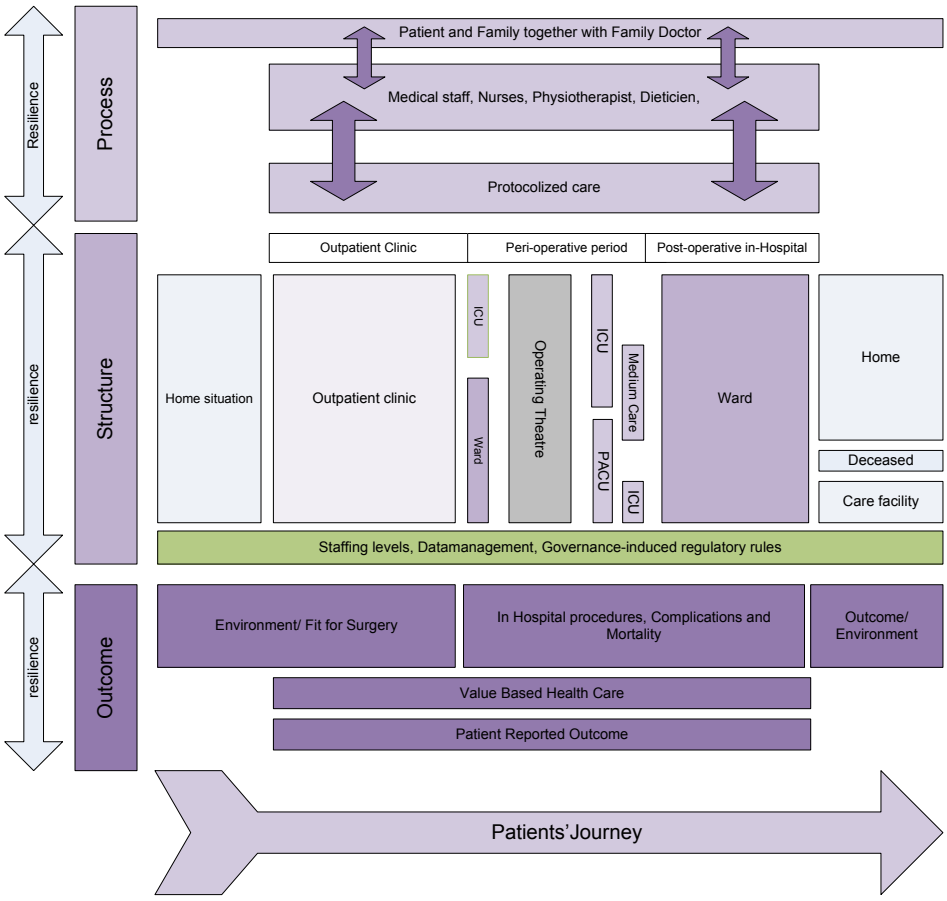
ized by its own set of variables which may have an impact on different levels during the patients' journey. These domains are not isolated, but intertwined and they affect each other. In the "process" domain we can identify patients and their families in interaction with careproviders in the hospital. The treatment and care process is based on protocols and guidelines which are often developed within one discipline. The "structure" domain is very much related to the organization and even architecture of a hospital. The patients' journey through the "Structure" domain will be through different departments and often starts at the outpatient clinic or the emergency department. If the hospital has a high-tech operating theatre for high-risk surgical procedures, staffing levels on the wards should be sufficient in relation to the peri-operative care needed for these complex procedures. A decision to raise the volume of specific high-risk surgical procedures will also have an impact on the use or number of ICU beds needed, as well as on staffing levels. "Outcome" is the third domain. Outcome will often focus on disease related or surgical procedure related morbidity and mortality, or ICU or hospital length of stay. While these are relatively easy to determine, Patient Reported Outcomes Measures (PROMs) and Value Based Health Care (VBHC) are more recently reported outcome measures. PROM focuses on quality and efficiency of care(14). VBHC dictates that care has to be organized around medical conditions and care cycles and needs to provide additional value to the patient and risk-adjusted outcome and cost should be measured(15). All domains have a form of resilience within their own compartment and will react if the content changes in one of the other compartments, e.g. expansion in the compartment of structure will have an impact on process and/or outcome compartments (Figure 1).

Modification of variables in the Donabedian Structure System can be an advantage or disadvantage for the individual patient. Structure interventions such as nurse staffing, closed format intensive care organisation, high-tech equipped operating theatres or procedure volumes are all related to outcome. A structure intervention, reflecting the setting in which care is being delivered, is dependent of choices made by the hospital board and staff, together with governance-regulation-rules. Structure interventions will have an impact on the total patient population and care-providers.

Process measures can be used to analyse provided care. For example, analysis of complications can be used by clinicians to identify which processes have been followed (or not), and how this affected the outcome of the patient. In the ideal organisational system, Prepare-Act and Reflect Cycles (P-A-R-cycle) or Plan-Do-Check-Act cycles are used to monitor provided care and outcome. As a result, these differences will be analyzed and reflected on in the multidisciplinary treatment team and, if necessary, changes will have to be made in treatment protocols or team processes and the P-A-R-cycle can start all over again (16). In health care, especially in hospitals, P-A-R-cycles are an instrument used to analyse ward or department

performance and are often part of audits or (near) adverse event analyses. Apart from these, mainly incident-driven, actions, repetitive P-A-R-cycles, organized by clinical-leaders, supplying feedback to care-providers with the intention to improve given care are scarce. Actual provided care to patients will be influenced by adherence to protocols by individual care-givers (physician, nurse, physiotherapist, etcetera) and available resources(10). Adherence to these protocols and guidelines relating to a specific medical intervention or medical condition is often not measured, or part of a P-A-R-cycle on the ward. As a result the cause of differences in provided care and outcome remain often unknown to care-givers. More feedback is needed, so that it will become clear that actions in these three domains will all influence the patients' journey and outcome (17).

Figure 1: Structure, process and outcome flowchart for high-risk surgical procedures.



An example of a process intervention is the "Enhanced Recovery After Surgery (ERAS)" program. After thorough analysis of the aspects in peri-operative care, relating to morbidity and mortality following colorectal surgery, Kehlet et al (18) developed the ERAS program, as a multimodality intervention to reduce post-operative complications and in-hospital Length of stay (LOS). Since the 1990s, ERAS has been implemented in many hospitals and aspects of the ERAS protocol have been adopted and implemented in the peri-operative care of high-risk surgical procedures (19-22). Unfortunately, knowledge of compliance to the ERAS protocol is unknown in most hospitals and seldom part of research questions (23, 24).

The setting of ICU-related care for high-risk surgical procedures

The adagium: "doing the right things right" is, for most physicians and nurses, an intrinsic motivator and essential in a team that provides care for high-risk surgical patients. Development and implementation of medical and nursing protocols is often a mono-disciplinary intervention or intra-disciplinary effort by physicians or nurses. This hampers the use of these different protocols in a multidisciplinary continuous system, such as is the case in the high-risk patients' journey. Because of the simultaneous use of many different clinical algorithms, protocols, guidelines and decision (making) rules of different departments and teams, the peri-operative process for the high-risk surgical patient becomes a labyrinth for care-providers and patients. This complexity increases even more in one hospital system with both high volume procedures like cardiac surgery, and low volume complex surgery such as pancreatico-duodenectomies and esophagus resections. Clearly, everybody agrees that each individual patient must receive safe and well organized care under all circumstances, but in a complex environment, this can be a difficult aim.

Clinical Pathways

Clinical Pathways, or Care pathways, are developed to provide optimal care for a specific patient group and to overcome differences of provided care between individual patients and individual care-providers. Development and implementation of these clinical pathways are considered complex process interventions and are usually accomplished in predictable non-complex procedures.

In the 1990s 'Clinical Pathways' (CP) or 'care pathways' were developed to integrate nursing and medical protocols into multidisciplinary care plans for low- and intermediate-risk surgery in the hospital. Development and implementation of a CP is a process intervention based on best practice rules, guidelines and available evidence based medicine. CP were originally designed to balance the quality of care and costs, by focusing on better use of resources, a maximum quality of care and minimization of delay in diagnosis and treatment (25). The content of a CP does not consist of multi-disciplinary or intra-disciplinary protocols and

best practices alone, but is also a 'day-to-day' care plan describing all care, interventions or activities needed to be achieved within a specific period of time to provide optimal patient care. A CP is specific to a medical condition, patient group or medical intervention, such as an operation. Evidence based medicine and best practice guidelines, developed as Work-as-Imagined, are often the building blocks for a team of caregivers to start the development of a CP. Together with these building blocks, available resources in the system, team culture and daily processes have to connect with each other to make the transfer from protocol or guideline to a CP. Different CPs for various medical conditions may coexist in a department or health care facility.

Many CPs have been developed, especially for predictable trajectories, where clinical interventions must be provided in a timely manner, and this implies that a CP is often a day-to-day care plan for a specific disease or medical procedure (26). So far many CPs have been developed for high volume, low- and average-risk healthcare procedures to reduce variations in care, complications, length of stay (LOS) and costs (27-30). Clinical pathways with the aim to standardize care and to reduce variation in care and outcome are also well known in, e.g. cardiology and pulmonology. CPs in cardiology, mainly focus on management of acute coronary syndromes and reduction of time-to-stent or time-to-surgery. Implementation of a CP for the treatment of acute coronary syndrome resulted in improved protocol adherence and improved outcome (31-33). The European Pathway Association performed an international multicenter cluster randomized controlled trial in 22 hospitals with the aim to reduce 6-month readmission rates after COPD exacerbation. Although 30-day readmission was significantly reduced without a reduction of 6-month readmission, evidence-based key interventions were better performed after implementation of a CP compared to usual care (34). CPs in day-care surgery, hip surgery, hysterectomy and colorectal surgery show reductions of postoperative morbidity and LOS as well (35). The evidence is growing that CP implementation has a positive effect on clinical outcome, however, reluctance to implementation of CPs still exist. This reluctance is often related to fear of loss of autonomy and aversion to over-regulation(36, 37).

A process intervention like the development and implementation of a CP for high-risk surgery could potentially reduce serious complications and LOS. Currently, many complex CP's in high-risk surgery do not include the ICU period in their CP, or only aspects of ICU care are implemented such as mechanical ventilation or care bundles like the treatment of sepsis and septic shock (38-44). Unfortunately, CP literature describing the total clinical patients' journey of the high-risk surgical patient, including the ICU period, is not available. The ICU is a very dynamic environment with very unpredictable responses of patients to treatment. High-risk surgical patients with a need for the ICU in the direct postoperative period could theoretically also benefit from CP guided care during their ICU stay. A CP

in the ICU could be a uniform protocol together with an hour-to-hour written schedule for a specific group of patients. This schedule should focus on recognition of deviation from the pathway by the attending nurses and should enable them to start immediate treatment within the boundaries of prescribed variances. The development, implementation and evaluation of a CP in the ICU should be part of a PAR-cycle and should be dynamic. Structure interventions in the system, together with changes in guidelines or resources, could affect WAD relating to the CP. This should result in agile adaptations of the content of the CP. We need to be aware that the ICU is not an isolated department. A process intervention in the ICU, like implementation of a CP, may affect the outcome in other departments that the patients will visit during their journey. Process and structure interventions in other departments at the same time, could also have an effect on the patient's journey. This will not be noticed if the intervention is not communicated, or part of the same P-A-R cycle.

Aims of this thesis

The aim of this thesis is to analyse the process intervention of development and implementation of clinical pathways in different high-risk surgical procedures relating to the ICU. This thesis aims to answer the following questions:

- Is it possible to develop and implement a nurse-driven clinical pathway, together with a variance report, to start treatment, within legal boundaries, in the ICU for all cardiac surgery patients? If so, what will be the effect on protocol adherence?
- Can this CP in high-volume, high-risk cardiac surgery patients be used as a blue-print for the development of low-volume, high-risk surgical procedures such as Pancreatico-duodenectomy and esophagectomy that will be used in the ICU, Post Anaesthesia Care Unit (PACU) and gastro-intestinal surgical ward?
- Can a CP be sustainable in high-volume cardiac surgery?
- Does preoperative optimization in the ICU effects outcome in low-volume high-risk esophageal surgery?

The outline of this Thesis

This thesis consists of two parts. The first part focuses on feasibility of a postoperative hour-to hour CP in the ICU, including the analysis of facilitators and barriers within the process. We will also focus on trends over time after implementation of a CP in high volume high-risk surgery. The second part of this thesis focuses on the development and implementation of CPs in low volume high-risk surgical procedures.

The process intervention of the development, implementation and evaluation of a post-operative clinical pathway based on a uniform protocol, together with an hour-to-hour written schedule (coined 'Radboud variance report'), for all cardiac surgery patients in the

intensive care unit is described in **Chapter 2**. This CP, in this high volume patient group, describes all multidisciplinary activities of the postoperative ICU processes and focuses on recognition of deviation from the pathway by nurses and their treatment within the boundaries of the prescribed variances. The aim of this study was to develop and implement a CP for all cardiac surgery patients in the ICU and to achieve a protocol adherence above 80%. In addition, we analysed the results of protocol adherence related to outcome in the intervention group and a matched historical control group treated according to the existing nursing and medical protocols in the year before the implementation of the CP. Following implementation of a postoperative CP for cardiac surgery patients we studied trends and outcome changes over time in the total group of over 7500 cardiac surgery patients treated in the nine years after the implementation of the CP. This study is described in **Chapter 3**. Primary aim of this study was to determine trends over time regarding inclusion and exclusion of patients in the CP. Secondary aims included determination of the trends over time relating to hospital length of stay, re-operations, ICU readmissions, hospital mortality and 1-year mortality between patients treated according to the CP and patients excluded from the CP. Subgroup analyses were performed between groups and for patients with a high Log EuroSCORE > 10, regarding distribution trends over time and clinical outcome.

In the **fourth chapter** we describe an observational evaluation study in a group of patients treated with an open transhiatal esophagectomy for carcinoma or high-grade dysplasia. This low volume group of high-risk surgical patients was pre-operatively optimized in the ICU according to an optimization matrix. We studied the association between pre-operative optimization and processes of care, as well as a comprehensive set of complications in a selected group of patients and compared this intervention group with a historical control group treated without pre-operative optimization in the two years prior to the intervention. The primary outcome was length of stay in hospital as an overall outcome measure of changes in post-operative morbidity. Our hypothesis was that pre-operative optimization in a selection of low volume, high-risk surgical patients would result in improvements in post-operative morbidity and mortality. This ICU intervention was a first step in the development of a CP for esophagectomy patients.

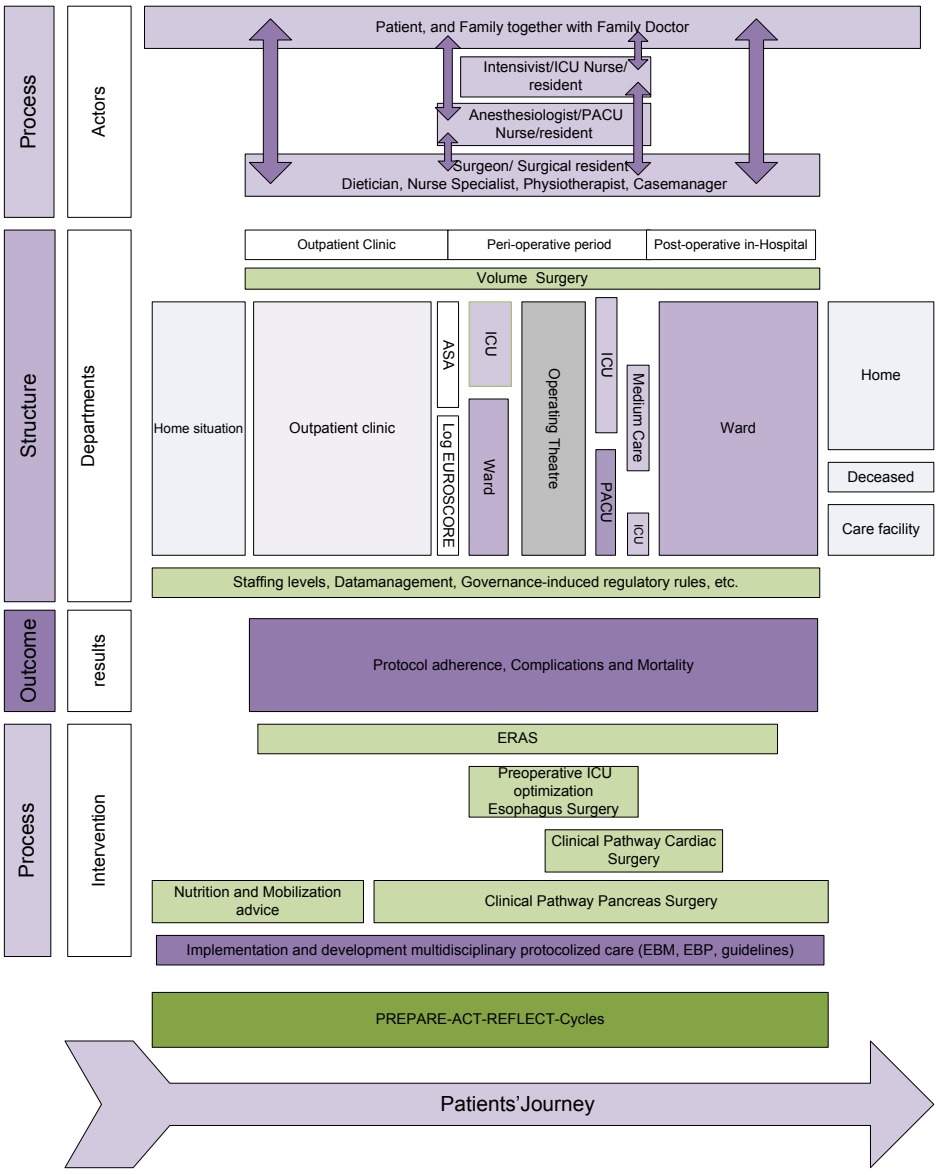
The postoperative ICU related CP and variance report for cardiac surgery was used as a blue print for development of a CP in the ICU and in the Post Anaesthesia Care Unit (PACU) for pancreatico-duodenectomy procedures. This process of development and implementation is described in **Chapter 5**. The pancreas CP had to be a continuum from admission to discharge from the hospital. Essential elements included: restrictive intra-operative fluid use, strict pain control, early mobilization, early drain and gastric tube removal, and early enteral feeding, all according to the ERAS protocol. Post-operatively, early warning scores

(EWS) were measured at least once during every 8 hour shift and additionally whenever indicated by the nurses, with strict directives for action by nurses according to the variance report. The incidence of post-operative complications was the primary endpoint to determine if implementation of the CP was safe and effective. Secondary endpoints were postoperative fluid balance, gastroparesis, protocol adherence to mobilization, drain removal, radiologic and surgical re-interventions, ICU readmission, in hospital-LOS, hospital readmission and mortality rate. **In chapter 6** we present a small overview of the literature on CPs in high-volume, low- and average risk procedures. Together with a reflection on a possible need for sustainable clinical pathways in high-risk surgery and the development of personalized care pathways in the near future.

In **Chapter 7**, we summarize the results of the work described in this thesis. **Chapter 8** comprises the general discussion and future perspectives. We focus on the relation between process interventions like the development and implementation of clinical pathways and outcome. Well- known facilitators for implementation and protocol adherence, such as clinical leadership and feedback cycles for care-providers, were also identified in our ICU and wards. Which barriers could we identify and were these overcome or bypassed before a CP implementation could start. Clinical pathways can be a tool in Work-as-Done in high-risk surgery to increase protocol adherence, together with a variance report. Although not the focus of the study, trends in behaviour and trends in protocol adherence of care-providers will be discussed. Future perspectives for process interventions like clinical pathways integrated in hospital processes and system interventions like data management could have a positive impact on quality of care and patient safety. Implementation of shared decision making and person-centered-care, developed in co-creation with care-providers and patients in the near future, will lead us to the clinical pathways 3.0.

Figure 2 shows the timing of our CP interventions in relation to the patients' journey together with the actors in the process.

Figure 2: Intervention Flowchart High-risk surgery related clinical pathways.



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Development and implementation of a clinical pathway for cardiac surgery in the intensive care unit: effects on protocol adherence

Marion van der Kolk, Mark van den Boogaard, Corine ter Brugge-Speelman, Jeroen Hol, Luc Noyez, Kees van Laarhoven, Hans van der Hoeven, Peter Pickkers

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Abstract

Rationale, aims and objectives

Cardiac surgery (CS) is facilitated by multiple peri-operative guidelines and protocols. Use of a clinical pathway (CP) may facilitate the care in these patients

Methods

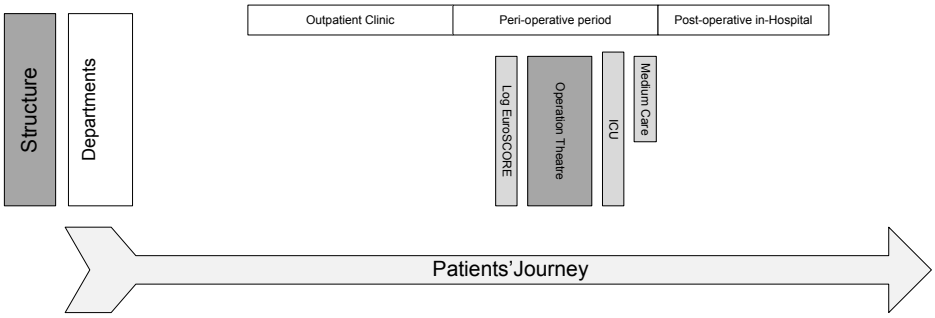
This is a pre-post design study in the ICU of a tertiary referral centre. A CP for CS patients in the ICU was developed by ICU-nurses and enabled them to execute pro-actively predefined actions in accordance with and within the preset boundaries which were part of a variance report.. A tailored implementation strategy was used. Primary outcome measure was protocol adherence above 80% on the domains of blood pressure control, action on chest tube blood loss and electrolyte control within the CP.

Results

In a four month period 84 consecutive CP patients were included and compared with 162 matched control patients admitted in the year before implementation, three patients were excluded. Propensity score was used as matching parameter. CP patients were more likely to receive early adequate treatment for derangements in electrolytes (96% vs 47%, $p<0.001$), blood pressure (90% vs 49%, $p<0.001$) and more timely treatment for chest tube blood loss (90% vs 10%, $p<0.001$).. We found no differences in hospital and ICU length of stay, ICU readmission or mortality.

Conclusion

Use of the CP improved postoperative ICU treatment for cardiac surgical patients. Implementation of a CP and the use of a special variance report could be a bleu print for the implementation and use of a CP in low volume high complex surgery.



Introduction

Cardiac surgery is considered high-risk surgery and is facilitated by multiple peri-operative guidelines and protocols (1). In the USA over 350.000 patients are treated annually for coronary bypass graft or a cardiac valve procedure with an overall mortality rate of 3-4% (2). While multidisciplinary teamwork for these patients is essential, the current protocols are mainly mono-disciplinary, limiting their integration and transparency. The actual use of these protocols in daily practice is unknown and compliance to these protocols is seldom measured (3)(1). We considered that the use of a clinical pathway (CP) facilitates the care of this specific group of patients by increasing compliance with existing protocols (4,5). Key elements of a CP are evidence based guidelines, clinical protocols and best practice rules, together with a coordinated sequence of activities of the multidisciplinary team (6). Many CPs have been developed for high volume, low- and average-risk health care procedures to reduce complications (7-9). In cardiac surgery some CP's for specific operations are being used, however, general CP's applicable to all cardiac surgery patients are not available (10-13). In addition, many complex CP's in high-risk surgery do not include the intensive care unit (ICU) period in their CP (14).

The ICU is a very dynamic environment, one patient can be hemodynamic or respiratory unstable and this can result in a delay in the treatment of less urgent situations for other patients in the ICU. To reduce delay, we developed a clinical pathway (CP) with a uniform protocol and an hour-to-hour written schedule for all cardiac surgery patients. The CP focused on recognition of deviation from the pathway by nurses and their treatment within the boundaries of the prescribed variances. The aim of this study was first to develop and implement a CP for all cardiac surgery patients in the ICU and to achieve a protocol adherence above 80%. Second, to determine the effects of this CP on patient outcome.

Methods

Setting and patients

The Radboud University Medical Centre in Nijmegen is a tertiairy referral center and is a 960- bed university hospital with a closed format ICU with 32 beds with 14 ICU-beds dedicated to approximately 800-1000 admitted cardiac surgery (CS) patients per year. ICU-nurses caring for cardiac surgery patients in the ICU are working in close cooperation with the medical staff.

Development of the Clinical Pathway

For the development of the CP it was important to identify potential barriers and facilitators in this particular setting and tailor the implementation strategy accordingly. Nursing and medical protocols for cardiac surgery patients in the ICU were examined and redefined, when available based on Evidence Based Medicine and Evidence Based Practice. The variance report was developed in close relationship with the Clinical Pathway Protocol by the two senior nurses (MvdB and CtB-S) and in cooperation with the medical and nursing staff. As part of the evidence based implementation strategy a small group of key-nurses reflected on the concepts of the CP and variance report and as part of a Prepare-Act-Reflect Cycle, they developed together with the senior nurses the variance report and CP. The described actions in the variance report were made in close cooperation with the medical staff and were synchronized to the medical protocols. '

Three features of our CP are distinctive compared to regular CP's. First, the CP was developed for all adult CS patients, irrespective of the type of cardiac surgery. Second, instead of a "day-to-day-care" plan, an "hour-to-hour" care plan was developed for ICU care. Describing all multidisciplinary activities needed to be achieved within a specific period of time, in a specific group of patients. Third, in the CP, a special variance report ('Radboud variance model'; appendix) was incorporated. This model enables nurses to execute predefined actions in accordance and within the preset boundaries of a variance protocol, without the need to consult the responsible physician first. (Dutch law and order for health care professionals BWBR0006251 chapter IV, article 35). This nurse driven CP not only included the recognition of minimal changes in physiology but also prescribed that recognition of these changes had to be followed by treatment in accordance to the variance report. The study was carried out in accordance with the applicable rules concerning biomedical research using patient information. Patient data were collected and analyzed anonymously.

Implementation of the Clinical Pathway

Awareness that implementation of a clinical pathway will introduce an essential change in daily practice for ICU-nurses and doctors is essential during development and implementation. A small group of key-nurses evaluated the concepts of the CP and the 'key' nurses were trained in the use of the CP. Feasibility of this nurse-driven clinical pathway for CS patients was studied during a period of two months. The project and the development status were discussed in team meetings and daily practice and feedback was welcomed by the developers. After two months we concluded that it was feasible and safe to use the CP and variance report in this patient group. Training of all ICU-nurses in the use of the CP and the variance report together with bedside teaching started on the ward. Physicians followed a separate training program about what the CP and the variance report entailed and the change in daily work process. After the information and training period the implementation started. Postoperative CS patients could only be treated according the CP when 'key-' nurses or senior nurses were on the ward for supervision. Monthly evaluation of the implementation process was part of the implementation process and did focus on barriers and facilitators of the implementation and on protocol adherence according to the variance report. Protocol adherence had to be above 80% and actions on deviations according to the variance report had to be within 30 minutes.

Design

After the implementation of the CP a matched cohort study was performed to determine protocol adherence in a group of ICU patients treated according to the CP for cardiac surgery patients. Covariates were used as predictors in a logistic regression analysis as being in the CP cohort or not. The included covariates, were type of operation, APACHE-II score, log EuroSCORE, COPD, diabetes, age and gender. The match was performed on three decimal places for the predicted probability (propensity score) and subsequently tested using the student T-test. Our conclusion was that there was no significant (p-value of ≥ 0.2) difference between the control group and CP group and therefore considered as good match between the two groups. In order to improve the power of this study a 1:2 matching design was used.

Control Group of Non-Clinical Pathway cardiac surgery patients

Non-CP patients treated on the ward during the implementation period were not used as controls because the risk of crossover contamination. The CP patients were matched to historical control patients operated one year before implementation. Except for the implementation and use of the CP there were no other relevant changes in therapy or treatment between both periods. Protocols and target values for e.g. protective mechanical ventilation, prevention of ventilator associated pneumonia, blood pressure regulation, strict glucose and electrolyte regulation did not differ between both groups.

End-points

To evaluate protocol adherence of the CP and the effects of implementation of the CP for CS patients in the ICU, the following predefined end-points were set: Incidence of temperature drop >0.3° C after ICU arrival, percentage of patients adequately treated if glucose and electrolytes were out of range, percentage of patients adequately treated if mean arterial pressure was out of range within 30 minutes, percentage of patients adequately treated within 30 minutes for postoperative chest drain blood production. We considered that protocol adherence to the CP should be above 80%. Also, other outcome effects of adherence to a nurse-driven CP including time to extubation, troponin and lactate levels, diuresis and time to mobilization were measured. Finally, ICU-length of stay (LOS), hospital-LOS, ICU readmission, and mortality rate were determined as secondary measures, as this study was not powered to detect a difference between groups in these endpoints.

Data collection:

Data was obtained via patient's medical records, including all ICU registrations which was similar for both groups. The 24-hour physiology registrations consisted of hemodynamic and respiratory parameters, levels of pain, fluid infusions, diuresis, and thoracic tube blood loss. Interventions like start of insulin, potassium infusion, vasopressors etc. were registered from the same 24-hour medical records. Although some data of the CP group was directly obtained from the CP list, including the variance report and were part of patients' medical record, these were the same data as was collected for the control group.

Exclusion criteria

Patients were excluded if there was no 'key-nurse' or senior nurse was available at the moment of post operative arrival at the ICU Patients with per-operative hemodynamic instability or ongoing hemodynamic instability during the first postoperative hours or with high doses of inotropic support or necessary re-operation, were excluded from the CP. The attending nurse and intensivist made the decision for exclusion together.

Statistics

Continuous variables were described as median and interquartile range [IQR, first and last quartile] and tested with the Mann-Whitney U test. Differences in dichotomous variables were analyzed using Chi-square test. Due to the exploratory nature of this study, and to increase the sensitivity to detect differences between groups, no correction for multiple testing was performed. Since the primary aim of the study was to achieve improvement in protocol adherence this was used for sample size calculation. To detect an increase of 20% in protocol adherence following the implementation of a clinical pathway, calculating

from α=0.05 and a power of 90%, the calculated sample size was 81 patients for the CP group and 162 patients for the control group. Covariates were used as predictors in a logistic regression analysis as being in the CP cohort or not. In order to improve the power of this study a 1:2 matching design was used.

This study was not powered to detect an effect of CP implementation on LOS-ICU, Hospital LOS and mortality. All statistical analyses were performed using SPSS version 20.01 for windows (IBM, SPSS statistics, Chicago, IL, USA).

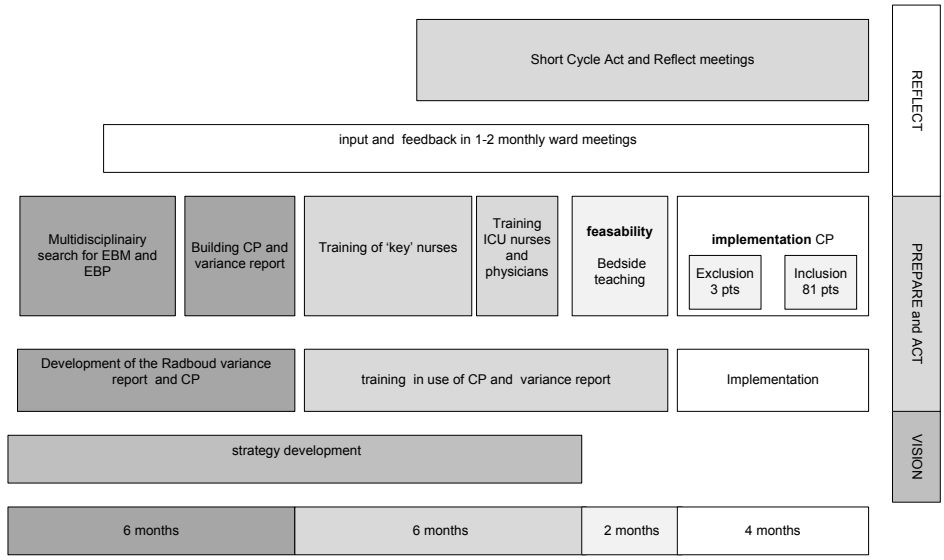
Results

Development period.
The wish to develop the clinical pathway was initiated by the ICU-nurses, as they wanted to have more clinical responsibilities. Development of this evidence based clinical pathway together with a variance report needed a period of six months. After this period education and training of nurses and doctors started together with a pilot period to find out if a CP for all cardiac surgery patients in the ICU was feasible

Implementation period.
Prior to the implementation of the clinical pathway, a barrier-facilitator analysis was performed. A negative attitude existed against more protocolizing their nursing work. Special attention was paid for this issue during the implementation training and during bedside training. During the implementation training it was recognized that the CP gave more guidance. Furthermore, ICU-nurses acknowledged that this CP together with the Radboud model variance report, empowered their work. More swift actions on deviations and availability of key-nurses made the implementation of the CP for cardiac surgery a positive experience. Concerning the facilitators, several ICU-nurses ,as well as the head of the medical staff contributed to the development of the CP and the variance report. These nurses served as key-nurses and the head of the medical staff approved clear and safe borders for making treatment decisions by nurses. Clinical decision making was not compulsory. When an intervention was needed as determined in the CP, nurses could always consult a physician in case they felt uncomfortable about the action they had to start according to the variance report.

After this intensive training period the CP for all cardiac surgery patients was implemented in daily practice accompanied with training on the job performed by the key-nurses and the CP developers. The total period of development, training, feasibility testing and implementation was 18 months (Figure 1).

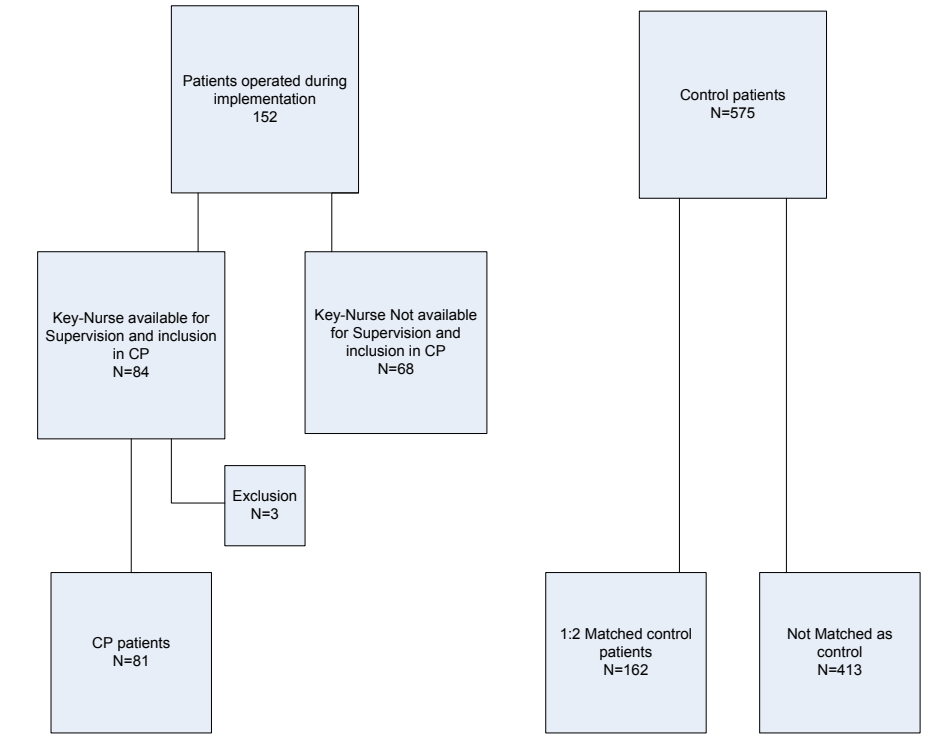
Figure 1: Flowchart implementation



Patients

During the four month implementation period, 152 patients underwent cardiac surgery. 84 patients arrived at the ICU after the operation when a senior nurse or 'key-nurse' was available for supervision. Three patients were excluded by mutual decision of the intensvist and the key-nurse because of post-operative instability with high dose of inotropics. The remaining 81 CP patients were matched with 162 non-CP patients (Figure 2).

Figure 2: Flowchart inclusion in Clinical Pathway



There was no significant difference in gender, age, type of operation, APACHE-II score and Log EuroSCORE between the two groups and these demographic characteristics are depicted in (Table 1).

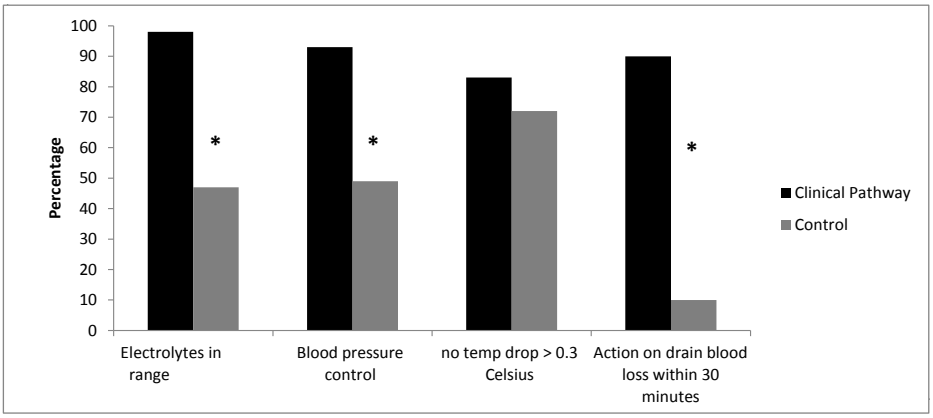
Table 1 :Demographic and patients' characteristics

	Clinical pathway (n=81)	Control (n=162)	Difference p-value
Male, N (%)	70 (86)	132 (82)	0.59
Age in years, median [IQR] Mean (SD)	64 [58-68] 60.8 (11.8)	63 [58-67] 61.2 (9.3)	0.85
Operation type, N (%)			
- CABG	55 (68)	109 (67)	0.78
- Valve	15 (19)	30 (19)	0.89
- CABG and valve	2 (3)	7 (4)	0.77
- Miscellaneous	9 (11)	16 (10)	0.94
APACHE II median [IQR]	13 [12-17]	13 [12-15]	0.42
Euroscore median [IQR]	3.0 [2.0-4.0]	3.0 [2.0-5.0]	0.67
Euroscore grouped:			
- 0 or 1	14 (18)	31 (20)	0.66
- 2	14 (18)	29 (19)	0.84
- 3	16 (20)	27 (18)	0.26
- 4	17 (22)	32 (21)	0.90
- greater than 5	18 (23)	35 (23)	0.99
Propensity score	0.33 [0.32-0.44]	0.33 [0.29-0.41]	0.20

Protocol adherence and effects on clinical outcome

The overall protocol adherence improved from mean 44% to 90% (p=0.01) after the implementation of the CP (Figure 3).

Figure 3: Percentage adherence to clinical protocol.



More patients in the CP group received early adequate treatment for derangements in glucose, electrolytes, according to the protocol. The incidence of temperature drop after arrival on the ICU was lower in the CP group. Protocol adherence for adequate and timely therapy within 30 minutes for blood pressure control and postoperative chest tube blood loss was higher in CP patients.. In addition, CP patients were extubated and mobilized earlier, and less patients in the CP group suffered from oliguria. Lactate and troponin levels were not different between the two groups. Also no differences were found for ICU and hospital length of stay, ICU readmission, and mortality (Table 2).

Table 2: Results of protocol adherence.

	Clinical pathway (n=81)	Control (n=162)	Difference p-value
Adherence to clinical protocol:			
- electrolytes N, (%)	79 (98)	76 (47)	<0.001
- blood pressure control N, (%)	74 (93)	80 (49)	<0.001
- no temp drop >0.3 Celsius, N (%)	67 (83)	115 (71)	0.21
- action on drain blood loss	28/31(90)	8/83 (10)	<0.001
- within 30 minutes N, (%)			
Mean percentage protocol adherence	90%	44%	0.01
Results related to outcome			
- extubation hrs median [IQR]	6.5 [5.0-9.4]	8.0 [6.0-12.0]	0.03
- troponin > 2.0 mcg/L N, (%)	65 (80)	129 (79)	0.77
- lactate >2.0 N, (%)	12 (15)	34 (21)	0.15
- diurese below minimum N, (%)	10 (13)	45 (28)	0.03
- mobilization in 24 hrs, N (%)	34 (42)	1 (1)	<0.0001
- LOS-ICU in hours, median IQR	22 [21-25]	23 [20-27]	0.21
- LOS-hospital in days, median IQR	7.0 [5.0-9.3]	6.9 [4.9-9.0]	0.66
- readmission N, (%)	3 (4)	13 (8.0)	0.66
- mortality N, (%)	0 (0)	3 (2)	0.46

Discussion

The main finding of the present study is that the use of existing protocols improves when embedded in a clinical pathway. We found that nurse-driven protocol adherence in the CP group was significantly better including some clinical outcome measures compared with the control group. To our knowledge this is the first study describing the implementation and use of a nurse driven postoperative CP in ICU patients which considers many aspects of postoperative ICU care, for all types of cardiac surgery. While many protocols exist for the post-operative care for cardiac surgery patients, the compliance to these protocols in daily clinical practice is troublesome and compliance is not measured routinely. Recently the American Association of Thoracic Surgery recognized the difficulty of implementation of guidelines, protocols and processes in an era of changing knowledge and consensus. Finding the facilitators and barriers is the first step in the development of a CP as described by Grol, Bosch and Evans-Lacko (15-17). Facilitators should be used to reduce the barriers in the system and help in building a successful CP.

Implementation of a CP

The development and implementation of a CP is a complex intervention. The multidisciplinary character is essential, facilitating the accommodation of different protocols, normally used by different disciplines. This implies that a culture change is an essential part of its implementation strategy. Importantly, a CP is limited to organize the care processes for a well-defined group of patients during a specific time period. Cardiac surgery patients may represent such a group with limited heterogeneity. Available CPs for cardiac surgery are only used for specific types of operation (e.g. coronary artery bypass graft or valve replacement) and exclude the care on the ICU. In contrast to general CP's using day-to-day care plans, our CP consisted of an hour-to-hour care plan and was nurse-driven. This study shows that despite the complexity of the post-operative cardiac surgery patient with the risk of rapid changes in his/her clinical condition, it is feasible to implement a uniform CP using a tailored and evidence-based implementation strategy. Support from management, clinical staff and "key-nurses", with adequate time for teaching and training, has probably been the cornerstone of this successful implementation.

Adherence to the CP

Determination of CP adherence during and following implementation is essential to establish its effects (18). In addition to the presence of key performance indicators, it is possible to determine adherence by the use of a variance report. In our study, all items measured, improved following implementation. Different from previous variance reports, in which only deviations or adverse events are registered, our variance model also allowed for pro-active interventions by the nurses within legal boundaries (19, 20). As a consequence,

the care for these patients obtained a more multidisciplinary character. It has previously been recognized that by giving the nurses a greater responsibility to execute medical protocols, the adherence to these protocols improves (21). In our view, their position in the current organization structure could be exploited to a greater extent. Therefore, the role of the nurses in the development and implementation of the protocol was emphasized in our study.

Outcome of patients following implementation of a CP

In view of the difficulties to demonstrate that use of a CP leads to improved outcome , it is generally accepted that enhanced process management without adverse effects on outcome can be considered a successful result of a CP (22, 23). We were unable to detect an effect on ICU and hospital LOS, or mortality in our CP patients, because of limited statistical power. Nevertheless, several clinical endpoints, including time to extubation, diuresis, and mobilization, improved significantly.

Limitations

Several limitations of our study need to be addressed. We started the CP in the ICU and this is only a small period of the hospital treatment of these patients. The most relevant limitation is the pre-post design nature of the study. The implementation of a CP is a change process for the team and the organization. Therefore, per patient randomization is not a feasible study design. To prevent crossover contamination we did therefore use a historical control group (patients admitted during the previous months) and not patients that were in the ICU but not in the CP during the same period on the ICU ward. Unfortunately, most studies on CP implementation share this limitation (24, 25).

Second, we aimed to demonstrate an effect on intermediate endpoints directly related to CP adherence and not on endpoints such as length of stay and mortality. It is important to realize that e.g. an effect on ICU length of stay will be difficult to achieve in this group of patients, as median ICU-LOS is 1 day, and patients will likely not be discharged from the ICU during night time, because discharge from the ICU outside office hours may have detrimental effects on outcome (26). Also mortality in cardiac surgery patients is relatively low, implying that a large number of patients will be needed to demonstrate a putative beneficial effect on survival. A third limitation is the short duration of our study, limiting the possibility to demonstrate that the change in culture is secured in the long-term. Recently, we have implemented our CP, including variance reporting, process indicators and measures of clinical outcome, in our patient data management system, facilitating sustained monitoring and feedback of adherence to the CP.

Conclusion

CP implementation resulted in more timely and better organized postoperative ICU treatment. This included an improved blood pressure control, electrolytes in range, temperature management, weaning from mechanical ventilation, and a more expedient adequate action to chest tube blood loss. We demonstrate that it is feasible to implement a predominantly nurse-driven hour-to-hour CP in the intensive care unit for cardiac surgery patients. This implementation strategy and variance report is a blue print for the implementation of a CP for low volume high risk surgical procedures.

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Sustainability of clinical pathway guided care in cardiac surgery ICU patients; nine years experience in over 7500 patients

B.M. van der Kolk, M. van den Boogaard, J.G. van der Hoeven, L. Noyez, P. Pickkers

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Abstract

Objective
To determine trends over time regarding inclusion of postoperative cardiac surgery intensive care unit patients in a Clinical Pathway , and the association with clinical outcome.

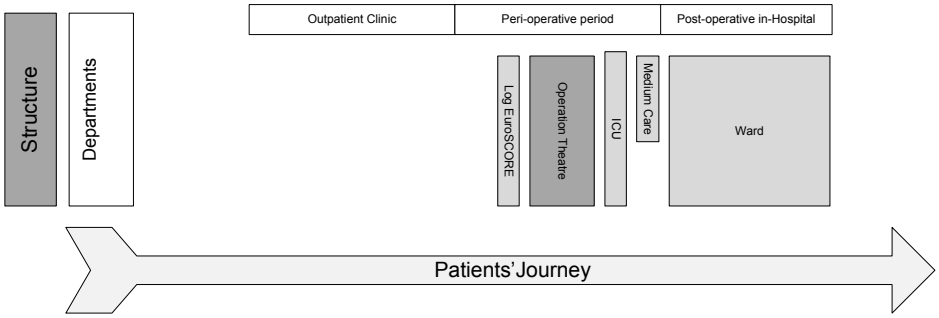
Design
Retrospective cohort study

Setting
Intensive Care Unit of an academic hospital.

Participants
All cardiac surgery patients operated between 2007 - 2015.

Measures and Results
A total of 7553 patients were operated. Three patient groups were identified: patients treated according to Clinical Pathway (n=6567), patients excluded from the Clinical Pathway within the first 48 hours (n=633), and patients never included in Clinical Pathway (n=353). Patients treated according to Clinical Pathway increased significantly over time from 74% to 95% and the median Log EuroSCORE (predicted mortality score) in this group increased significantly over time (p=0.016). In-hospital length of stay decreased in all groups, but significantly in Clinical Pathway group (p<0.001). Overall, the in-hospital, and 1-year mortality decreased from 1.5 to 1.1% and 3.7 to 2.9%, respectively (both p<0.05). Patients with a Log EuroSCORE >10 were more likely excluded from Clinical Pathway (p<0.001), but, if included in Clinical Pathway, these patients had a significantly shorter Intensive Care stay and in-hospital stay compared to excluded patients with a Log EuroSCORE >10 (both p<0.001).

Conclusions
The use of a Clinical Pathway for all postoperative cardiac surgery patients in the Intensive Care Unit is sustainable. While more complex patients were treated according to the Clinical Pathway, clinical outcome improved in the Clinical Pathway group.



Introduction

The annual need for cardiovascular procedures worldwide is estimated at over 12 million procedures (1), and over 400000 patients are operated in the United States for coronary artery bypass grafting or cardiac valve procedures, which is accompanied with an overall 30-days mortality rate of 3-4%(2). Cardiac surgery can therefore be considered as high-volume and high-risk surgery. Following the surgical procedure the journey of the patient starts in the intensive care unit (ICU). Postoperative care for these patients is facilitated by multiple guidelines and protocols. In the ideal situation, exchange of information and protocol use is optimal, resulting in a low post-operative morbidity and a low mortality rate. Multidisciplinary teams of physicians and nurses work together in the ICU, and therefore the use of transparent patient centered treatment protocols need to be considered as an essential component of postoperative care(3). It is thought that implementation of a clinical pathway (CP) for cardiac surgery patients in the ICU will improve transparency of multidisciplinary protocols in postoperative ICU treatment(4-6). While generally a CP indicates a 'day-to-day' care plan, in the ICU, a CP needs to be adjusted into an 'hour-to-hour' care plan, describing all multidisciplinary activities needed to be achieved within a specific period of time(7). Early and adequate treatment during the first postoperative hours may limit progression of organ damage and subsequently reduce morbidity and mortality(8-10). Therefore, intensive monitoring and treatment warrant a pro-active attitude and swift execution of interventions. As a consequence, most CPs for cardiac surgery patients explicitly exclude this postoperative ICU period(11, 12).

In our view, treatment according to a CP for postoperative cardiac surgery patients in the ICU is feasible. Therefore, we developed and successfully implemented an ICU nurse-driven CP, for all types of cardiac surgery patients based on evidence based medicine, evidence based practice and best practice guidelines (13). This CP includes a unique variance report ('Radboud variance model') describing all multidisciplinary activities in the

ICU for all postoperative cardiac surgery patients. This variance model enables nurses and residents to pro-actively execute, predefined actions in accordance with and within preset boundaries of a variance protocol, without the need to directly consult the responsible intensivist first. Previously, we performed a matched control study in 243 patients and found that nurse-driven protocol adherence in the Clinical Pathway group was significantly better, including some clinical outcome measures, compared with the historical control group. This study was not powered to detect a difference between groups in ICU-length of stay (LOS), hospital-LOS, ICU readmission, and mortality rate (13). Not all cardiac surgery patients will follow the complete duration of the CP and some may never be included. Currently, this exclusion is based on their clinical assessment, including an expected high-risk of dying in patients with a high Log EuroSCORE (14), or complications that occurred during the surgical procedure and the clinical expectancy that the CP should not be followed.
Long-term follow up of the use CPs following their implementation are sparsely described and as a result, sustainability of most implemented CPs are unknown (15). Therefore the primary aim of this study was to determine trends over time regarding inclusion and exclusion of cardiac surgery patients in the CP. Secondary aims included trends over time in ICU and hospital length of stay, re-operations, ICU readmissions, hospital and 1-year mortality and between groups. Subgroup analyses were performed between included and excluded patient groups and for patients with a Log EuroSCORE >10.

Methods

Design and patients

A retrospective cohort study was performed including all consecutive cardiac surgery patients aged ≥18 year, operated between January 1st, 2007 and December 31st, 2015. Patients that underwent a closed procedure (i.e. thoracic endovascular aortic repair procedure (TEVAR) or a transcatheter aortic valve implantation (TAVI) were not included.

In 2013 a new patient data management system (EPIC®, Verona, Wisconsin USA) was implemented in our hospital, in which an electronic CP for cardiac surgery patients was incorporated. Since we considered this as a relevant structure intervention, we also analyzed the effects of implementation of this Patient Data Management System (PDMS).

Setting

The ICU of the Radboud University Medical Center is a 32 bed closed format ICU with 10 beds dedicated for cardiac surgery patients. Annually approximately 900 cardiac surgery patients are treated postoperatively in the ICU. Intensivists, residents in training and ICU nurses treat these patients in close cooperation with cardiac surgeons and cardiologists.

Clinical pathway

The CP for cardiac surgery patients, including the variance report, was developed and implemented in the ICU in 2006, providing nurses the possibility to act within the boundaries of preset targets and within the legal borders of the Dutch law, without having to wait for approval of the supervising resident or intensivist (13). The variance report includes many interventions considering, e.g. early actions on low and high blood pressure, arrhythmia, early actions on thoracic tube blood loss. Following the implementation period, the adherence to the CP was above 80%, and it was considered as being successfully implemented. The implementation study was published elsewhere.The main finding was that, when embedded in a clinical pathway with a variance report, the use of existing protocols improves. Over 70% of the patients were included in the clinical pathway after the implementation (13). Prediction Models are important in cardiac surgery and ICU patients. For this study we used The European System for Cardiac Operative Risk Evaluation, EuroSCORE. It is a model to predict the risk of death and survival before cardiac surgery, taking into account the patient, comorbidity, and the proposed operation. Acute Physiology and Chronic Health Evaluation (APACHE) Score is a mortality prediction model for ICU patients and uses the worst physiologic parameters on day 1 in the ICU.

Monthly updates, regarding several outcome measures are provided to the ICU team. These reports give overall information of the total treatment group and reflect on time until extubation, ICU and in-hospital length of stay (LOS), hospital mortality and 1-year mortality. When changes in trends are observed, e.g. time until extubation, or time to discharge from the ICU, analysis according to a Prepare-Act-Reflect cycle (P-A-R-cycle) is performed (16). Whenever needed, teaching and guidance were tools of the P-A-R-cycle, if deviations were observed.

We identified three patient groups: group one was completely treated according to the CP ('Clinical Pathway patients'); group two consisted of patients that were initially included in the CP, but excluded within the first 48 hours after surgery ('Secondary excluded patients'). In this group, patients were often excluded due to too many or serious deviations from the normal course that needed direct treatment supervision by a resident or intensivist in close collaboration with the cardiac surgeon and/or cardiologist. Group three consisted of patients that were never included in the CP due to serious comorbidity or intra-operative complications and expectations that CP criteria for treatment could not be met (' never included patients'). All patients excluded from the CP, were treated according to the medical and nursing protocols also used in the CP, however, without using the preset CP targets. In CP-excluded patients, nurses and residents were not allowed to start the interventions as described in the 'Radboud variance report' without consulting the attending intensivist first, when clinical deviations were observed.

The implementation of the PDMS in 2013 was considered a complex structure intervention. We decided to analyse the effect of implementation of the PDMS, because we had the expectancy that the implementation of a new PDMS might affect all processes regarding patient information including care and safety. For this we used a shadow paper system alongside the PDMS for the purpose to be able to find all the patients according to their inclusion or exclusion group in the system and enable us to analyse them.

Data collection

Data for the monthly updates, as well as for this study were retrieved from the 'CORonary artery surgery database RADboudumc' (CORRAD) (17), and merged with the ICU data collected for the National Intensive Care Evaluation (NICE) registry (18). The CORRAD database primarily collects cardiac disease specific characteristics, cardiac surgical treatment data (e.g. type of operation, re-operation, blood loss), and CP data, while the NICE database collects ICU characteristics (e.g. comorbidity, severity of illness score, (APACHE-II and APACHE-IV scores), duration of mechanical ventilation, sepsis and other complications, etc).

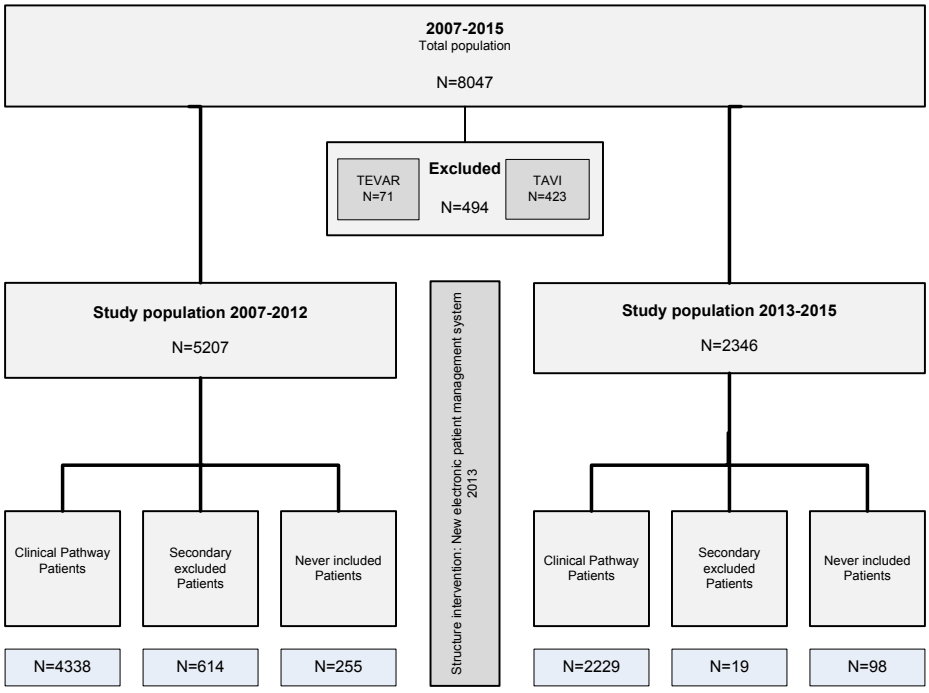
Statistical analysis

Continuous data are presented as mean with standard deviation (SD), or median with first and third interquartile range [IQR], depending on its distribution. Differences in continuous variables between more than two groups were tested with ANOVA with Tukey's post-hoc HS analysis, and Kruskall-Wallis with pairwise comparisons. Dichotomous variables were tested using Chi-square analysis. All statistical analyses were performed using SPSS version 22.1 for windows (IBM, SPSS, Chicago, IL, USA).

Results

Between January 2007 and December 2015, a total of 8047 patients underwent a cardiac surgery procedure. 7553 patients underwent open cardiac surgery and were postoperatively admitted to the ICU, and 494 patients underwent a closed procedure (TAVI or TEVAR). All 7553 patients treated with an open cardiac surgery procedure were included in this study. In the first period 2007 - 2012, a total of 5207 patients were included, and following the implementation of the new electronic PDMS, from 2013 - 2015, a total of 2346 patients were included (Figure 1).

Figure 1: Flowchart of the patient population 2007-2015.



Trends over time regarding inclusion and exclusion of cardiac surgery patients in the CP

The group of CP patients consisted of 6567 (87%) patients, the group secondary excluded patients consisted of 633 (8.4%) patients and 353 (4.7%) patients were never included in the CP. Analysis of the demographic characteristics between the three patient groups revealed that secondary excluded and never included patients had a significantly higher Log EuroSCORE, APACHE–II and APACHE-IV score (all $p<0.001$) compared to never included patients (Table 1). Patients operated for coronary artery bypass grafting (CABG), were more likely treated according to the CP ($p<0.001$) than patients for other cardiac surgical procedures. Patients with a Log EuroSCORE >10 were more likely excluded from the CP ($p<0.001$), (Table 1). In the CP group the Log EuroSCORE and APACHE–II score increased significantly over time, $p=0.016$ and $p<0.001$, respectively. Increase of the APACHE –II score was also observed in the never included patients (Table 1).

Table 1: Patient characteristics per study group over time, period 2007-2015.

	Period 2007-2009		
	Clinical Pathway patients N=1862	Secondary excluded patients N=307	Never included patients N=136
Age, mean (SD)	65 (11)[a b]	69 (10)[f]	59 (17)
Male, n (%)	1340 (72)[a]	192 (63)	88 (65)
Operation type, n (%)			
CABG	1291 (69)[a,b]	156 (50.8)[c]	52 (38.2)
CABG+Valve	203 (10.9)[a,b]	65 (21.2)[c]	18 (13.2)
Single valve	236 (12.7)[e,b]	48 (15.6)[c]	21 (15.4)
Thoracic aorta	39 (2.1)[a,b]	15 (4.9)[c]	17 (12.5)
Others	93 (5.0)[a,b]	23 (7.5)[c]	28 (20.6)
APACHE-II score, mean (SD)	13 (4)[a]	16 (5)[f]	14 (6)
APACHE-IV score, mean (SD)	Not available	Not available	Not available
Log EuroSCORE, median [IQR]	2.91 [1.54-5.71][a b]	5.85 [2.87-12-41][c]	7.16 [3.38-22.49]
Log EuroSCORE >10, n (%)	199 (10.7)[a,b]	91 (29.6)	56 (41.2)
Chronic Renal Failure, n (%)	33 (1.8)[e]	11 (3.6)	3 (2.2)
Dialysis, n (%)	5 (0.3)[e,f]	4 (1.3)	2 (2.5)
COPD, n (%)	186 (10)	42 (13.7)	15 (11)
Diabetes, n (%)	317 (17)	65 (21.2)	23 (16.9)
	Period 2010-2012		
	Clinical Pathway patients N=2476	Secondary excluded patients N=307	Never included patients N=119
Age, mean (SD)	66 (11)[d e]	68 (10)[f]	64 (13)
Male, n (%)	1794 (73)[e]	203 (66)	88 (74)
Operation type, n (%)			
CABG	1646 (66.5)[a,b]	148 (48.2)[c]	47 (39.5)
CABG+Valve	233 (9.4)[e,b]	67 (21.8)[c]	12 (10.1)
Single valve	436 (17.6)[a,b]	62 (20.2)[c]	25 (21)
Thoracic aorta	86 (3.5)[a,b]	13 (4.2)[c]	19 (16)
Others	75 (3.0)[a,b]	17 (5.5)[c]	16 (13.4)
APACHE-II score, mean (SD)	13 (4)[a b]	15 (5)	15 (6)
APACHE-IV score, mean (SD)	58 (33)[a]	77 (22)[c]	74 (29)
Log EuroSCORE, median [IQR]	2.97 [1.65-5.93][a b]	5.87 [2.70-10.66][f]	8.77 [3.67-20.38]
Log EuroSCORE >10, n (%)	273 (11.0)[a,b]	82 (26.7)	48 (40.3)
Chronic Renal Failure, n (%)	31 (1.3)[a,b]	17 (5.5)	6 (5.0)
Dialysis, n (%)	5 (0.2)[a,b]	8 (2.6)	3 (2.5)
COPD, n (%)	249 (10.1)[e]	52 (16.9)	11 (9.2)
Diabetes, n (%)	456 (18.4)	66 (21.5)	22 (18.5)

Table 1: Continued.

	Period 2013-2015		
	Clinical Pathway patients N=2229	Secondary excluded patients N=19*	Never included patients N=98
Age, mean (SD)	66 (11)	65 (12)	65 (11)
Male, n (%)	1608 (73)	11 (58)	64 (65)
Operation type, n (%)			
CABG	1308 (59.0)[b]	10 (52.6)	45 (46.9)
CABG+Valve	220 (9.9)	0 (0)	8 (8.3)
Single valve	445 (20.1)	4 (21.1)	18 (18.8)
Thoracic aorta	176 (7.9)[b]	2 (10.5)	15 (15.6)
Others	67 (3.0)[b]	3 (15.8)	10 (10.4)
APACHE-II score, mean (SD)	16 (4)[b]	16 (5)	18 (7)
APACHE-IV score, mean (SD)	61 (19)[b]	63 (13)	71 (31)
Log EuroSCORE, median [IQR]	3.30 [1.75-6.25][b]	2.73 [1.61-7.13][f]	6.05 [2.95-24.75]
Log EuroSCORE >10, n (%)	255 (11.8)[b]	2 (13.3)*	39 (40.6)
Chronic Renal Failure, n (%)	21 (1.0)	0 (0)*	2 (2.3)
Dialysis, n (%)	3 (0.1)[e]	0 (0)*	1 (1.2)
COPD, n, (%)	240 (11.5)	0 (0)*	8 (9.3)
Diabetes, n, (%)	420 (20.1)	4 (21.1)*	19 (22.1)

[a] Statistically significant (p<0.001) CP patients compared to secondary excluded patients.
[b] Statistically significant (P<0.001) CP patients compared to never included patients.
[c] Statistically significant (p<0.001) secondary excluded patients compared to never included patients.
[d] Statistically significant (p<0.05) CP patients compared to secondary excluded patients.
[e] Statistically significant (p<0.05) CP patients compared to never included patients.
[f] Statistically significant (p<0.05) secondary excluded patients compared to never included patients.

LogEuroSCORE: patients' predicted risk of death and survival prior to cardiac surgery, taking into account the patient, co-morbidity, and the proposed operation.

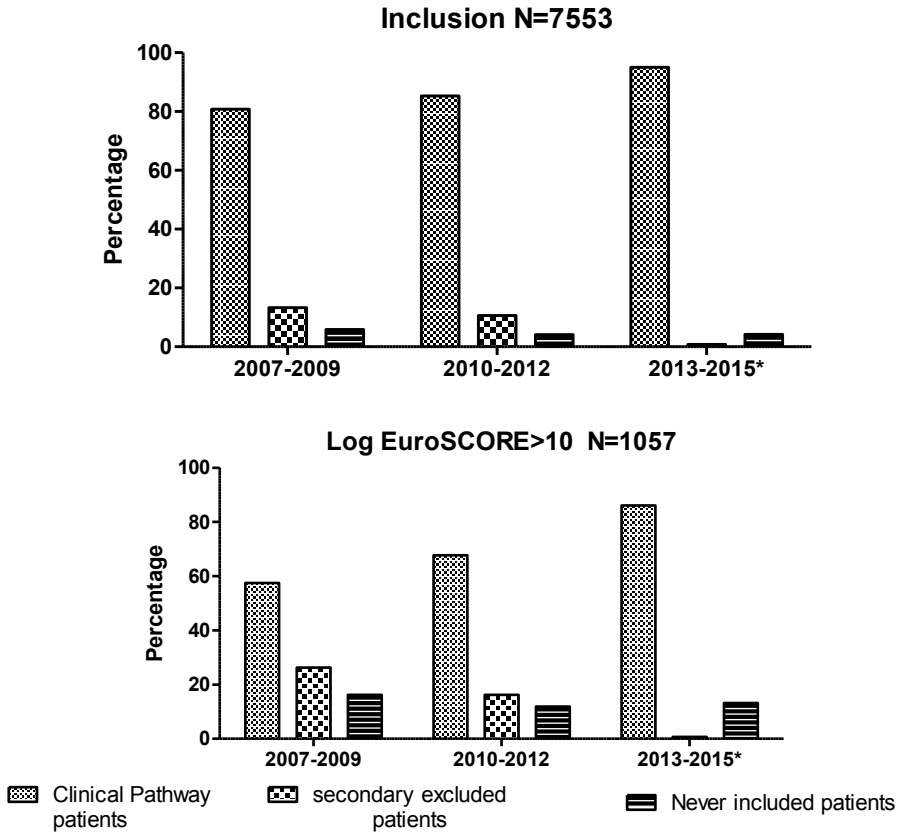
APACHE –IV score became available in our registration in 2010 therefore this score is not available in 2007-2009 data.

* In the group of secondary excluded patients, following implementation of the new PDMS, under-registration in this patient group occurred, as a secondary exclusion was not always recorded in the system.

Trends over time of the CP groups

Over time, the percentage of patients treated according to the CP increased from 74% in 2007 to 95% in 2012 and remained stable until the end of the study in 2015. The percentage of patients with a Log EuroSCORE >10 overall, did not increase during the study period (p=0.13). Over time significantly more patients with a Log EuroSCORE >10 were treated in the CP group, 58% to 86% (p<0.001). The increase of patients with a Log EuroSCORE >10 excluded from the CP, did not reach statistical significance in both groups (Figure 2).

Figure 2: Inclusion and exclusion CP and Log EuroSCORE >10 within groups.



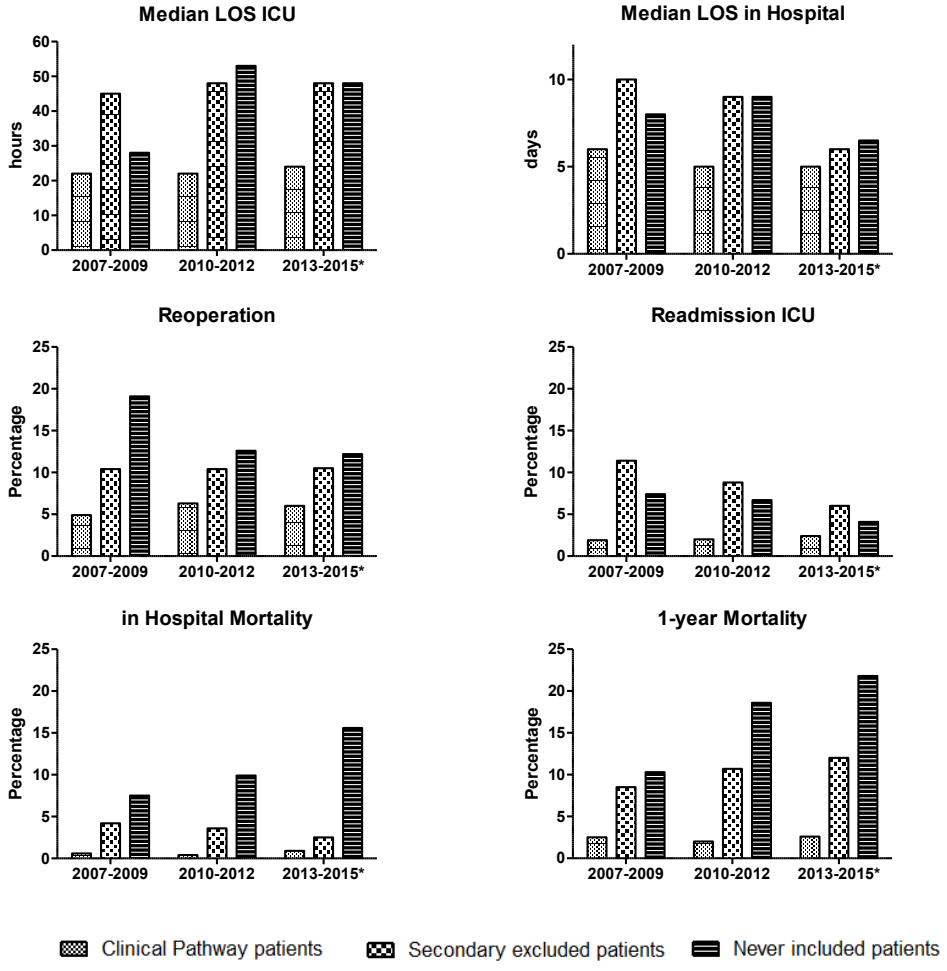
* :In the group of secondary excluded patients, following implementation of the new PDMS, under registration in this patient group occurred, as a secondary exclusion was not always recorded in the system

Outcome

The overall hospital length of stay (LOS) reduced significantly from median 6 days [IQR 5-9] to 5 days [IQR 3-7], ($p<0.001$). Over time the ICU readmission rate decreased from 3.6% to 2.4% ($p<0.001$). The hospital and 1-year mortality decreased from 1.5% to 1.1% ($p<0.05$) and 3.7% to 2.9% ($p<0.05$), respectively. Over time, less patients were primary excluded from the CP ($p=0.04$). In the CP group median ICU-LOS, in-hospital LOS and mortality decreased over time ($p<0.001$). In the primary excluded patients, ICU-LOS increased, while hospital LOS decreased (both $p<0.001$). The median ICU-LOS in the secondary excluded patient group did not change over time, while the in-hospital LOS decreased ($p<0.001$). The incidence of postoperative sepsis and acute kidney injury remained stable over the period, varying between 0.6-1.0% and 2.6-3.8%, respectively.

There seems to be a trend towards increase in mortality and 1-year mortality and a reduction in readmission ICU over time in the excluded patients (Figure 3 and supplemental Table 3).

Figure 3: Trends in outcome over time for CP patients, never included patients and secondary excluded patients divided per 3-year period for the total period 2007-2015 (n=7553).



Effect of Clinical Pathway in patients with a Log EuroSCORE >10

A total of 1057 patients had a Log EuroSCORE >10. These patients had a higher risk for complications and mortality, especially in patients that were not treated according to the CP (Table 2). Patients with a Log EuroSCORE >10 treated according to the CP had a shorter ICU stay and in-hospital LOS compared to those that were not treated according to the

CP ($p<0.001$). Time until extubation was shorter in patients treated according to the CP and in secondary excluded patients, than in never included patients ($p<0.001$) . In-hospital mortality and 1-year mortality were significantly lower in the CP group compared to excluded patients (both $p<0.001$) (Table 2).

Effects of implementation of patient data management system

We observed that for more than one year, registration and correct tagging of patients in the PDMS, according to their postoperative pathway was cumbersome. This resulted in an under registration of secondary excluded patients from the CP (Figure 1). Overall, implementation of a new PDMS did not influence the characteristics and outcome data within the subgroups.

Table 2: Demographic characteristics and results of patients with a Log EuroSCORE >10.

	Clinical Pathway patients N=732	Secondary excluded patients N=180	Never included patients N=145
Demographic characteristics			
Age, mean, (SD)	71 (11)	73 [66-79][a]	66 [60-75][a]
Gender, male n, (%)	400(55)	94 (52)	89 (61)
Type of operation.n,(%)			
CABG	232 (32)	53 (29)	29 (20)[a]
CABG+ Valve	140 (19)	44 (24)	18 (12)
Valve	178 (24)	39 (22)	38 (26)
Thoracic Aorta	137 (19)	24 (13)	44 (3)[a,b]
Others	45(6)	20 (11)	16 (11)
APACHE-II score, mean (SD)	16 (5)	17 (5)	18 (7)[b]
APACHE-IV score, mean (SD)	73 (23)	75 (26)	80 (30)
Left ventricle ejection fraction, median [IQR}	50 [40-60]	44 [35-50][b]	40 [30-50][b]
Log EuroSCORE, median [IQR]	15.0 [11.7-21.6]	18.4 [13.1-32.5][a]	26.9 [15.8-40.0][a]
Comorbidity n (%)			
COPD	109 (16.8)	25 (13.9)[a]	14 (9.9)[a]
Diabetes	119 (16.3)	34 (18.9)[b]	19 (13.5)
Chronic renal failure	25 (3.5)	12 (6.7)[a]	7 (4.8)
Dialysis	4 (0.6)	6(3.3%)[a]	3 (2.1)[a]
Postoperative results			
Time until detubation in hours median [IQR]	9 [7-13]	10 [7.5-15]	38 [11-99][a,b]
ICU-LOS (hrs), median [IQR]	24 [22-47]	72 [26-161][a]	96 [42-259][a,c]
Hospital LOS (days), median [IQR]	7 [5-13]	14 [9-26][a]	13 [8-27][a,c]
Postoperative complications and outcome			
Re-admission to ICU, n (%)	34 (4.7)	22 (12.2)[a]	12 (8.3)[a,c]
Acute Kidney Injury (AKI), n (%)	30 (4.1)	29 (16.1)	26 (18.4)[a]
Reoperation, n (%)	69 (9.4)	26 (14.4)[b]	33 (22.2)[a]
Postoperative blood loss during first 8-hrs in ICU (ml), median [IQR]	420 [240-760]	540 [308-793]	810 [400-1390][a,c]
In-hospital mortality, n (%)	22 (3.0)	16 (8.9.)	25(17.2)[a,b,c]
1-year mortality, n (%)	61 (8.3)	33 (18.3)[a]	35 (24.1)[a,c]

[a] p< 0.001 significantly different between patients not in the clinical pathway versus those treated according to the CP.

[b] p< 0.05 significantly different between patients not in the clinical pathway versus those treated according to the CP

[c] p< 0.05 significant difference between patients secondary excluded from clinical pathway and patients primary excluded from the CP group.

[d] p< 0.05 significantly different between patients secondary excluded from clinical pathway and those treated according to the CP.

Discussion

In the present study of a nine-year period experience with the use of a clinical pathway in cardiac surgery patients, we found that the percentage of patients treated according to the CP increased over time. While more complex patients with more co-morbidities were included in the CP, clinical outcome improved in patients treated according to the CP. The composition of the never included patient group consisted of more complex patients with clearly a higher risk for postoperative morbidity and mortality. This finding illustrates that care-givers can adequately select these patients.

Clinical pathway-guided care in the postoperative period has been implemented in many hospitals. However, usually these CPs do not include the ICU care. CP-guided care in cardiac surgery seems to focus on specific groups like CABG, TAVI and valve replacement surgery . The outcome measures mainly focus on reduction of morbidity and in-hospital LOS through goal-directed therapy in cardiac surgery (12, 19-21).

The introduction of a CP in our patient group, resulted in improved outcome related to in hospital LOS, readmission and mortality and are in accordance with findings in low- and intermediate-risk surgical procedures (22). Clinical pathways for standardized care to reduce variation in care and outcome are well known in e.g. cardiology. CPs in cardiology, mainly focus on management of acute coronary syndromes and reduction of time-to-stent or time-to-surgery. Implementation of a CP for the treatment of acute coronary syndrome resulted in improved protocol adherence (23), improved treatment, as well as improved outcome (24, 25). Currently, the implementation and use of a CP in cardiac surgery patients is not common practice and literature is scarce and mainly limited to specific aspects of care. Moreover, implementation of CP-guided care in the ICU is often not included (11). This is not specific to cardiac surgery, in many other high-risk surgery procedures, ICU care is seldom part of the CP (26-28). We implemented a CP for all post-operative cardiac surgery procedures in the ICU, together with an unique variance report, and showed that sustainability of CP-guided care after implementation over a nine-year period is feasible. This is the first study describing the sustained long term use of a CP for cardiac surgery patients.

Many structure interventions like data management, staffing levels and governance-induced regulatory rules will influence work processes and outcome related to these structure interventions (29). This has to be taken into account during follow-up, innovation and research of sustainable pathways. During our nine years' journey we had one structure intervention: the change of a PDMS, with impact on processes and members of the whole treatment team. Even though anticipated and pro-actively approached, including

training and a shadow paper system, we learned afterwards that some of the data were not easily traceable in the system.

More than 9 years after implementation, only 5% of our cardiac surgery patients is not included in the CP. Currently, a high Log EuroSCORE does not automatically indicate that this patient needs to be excluded from treatment according to the CP. Our clinical outcome data illustrates that it is feasible to differentiate the patients that were treated according to the CP from those who were not. Any change in the results and outcome measures in the different patient groups, initiates analyses of the procedures underneath and patient selection. Because the team knowledge and learning community of the ICU-nurses increased over time, we were able to start adjusting targets within the CP to individual patients, e.g for blood pressure.

Several limitations of the study need to be addressed. First, this is a retrospective cohort study and not a controlled trial, as a result this does not allow to draw firm conclusions that treatment according to the CP per se leads to a better outcome. The observed impaired outcome in patients not treated according to the CP is most likely the result of improved patient selection over time of the truly high-risk patients that were excluded from the CP. Nevertheless, we observed over time that an increasing percentage of cardiac surgery patients, up to 95%, can be treated according to the CP after surgery, without a negative effect on their outcome. Second, this is a single center study performed by a committed team, potentially limiting its generalizability. As with other changes in treatment and responsibilities, the barriers and difficulties of implementation are recognized.

In summary, the sustained use of a clinical pathway is a dynamic process and changes in the underlying evidence should also be part of the evaluation of a CP (30). This continuous learning process in CP-guided care will lead us to more personalized pathways for high-risk patients and to shared decisions in person-centered care in the future.

Conclusions

We showed that the use of a Clinical Pathway for all postoperative cardiac surgery patients in the Intensive Care Unit over time is sustainable. While more high risk and complex patients were treated according to the Clinical Pathway, clinical outcome improved in the Clinical Pathway group.

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Effects related to ScvO2-guided preoperative optimization in open transhiatal esophagectomy patients: an observational evaluation study

B.M. van der Kolk, M. van den Boogaard, G. Peeters, J.J. Bonenkamp, C.J.H.M. van Laarhoven, J.G. van der Hoeven, P. Pickkers

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Abstract

Background

Most studies on pre-operative optimization are in heterogenous high risk surgical patient groups and results suggest that interventions aimed to improve the hemodynamic condition may exert beneficial effects . Open transhiatal esophagectomy is associated with considerable postoperative morbidity and mortality. Pre-operative optimization of the circulation may result in a reduction of in-hospital-LOS, risk for anastomotic leakage and prevent infection/sepsis. The effects of pre-operative optimization in this group of patients are unknown.

Methods

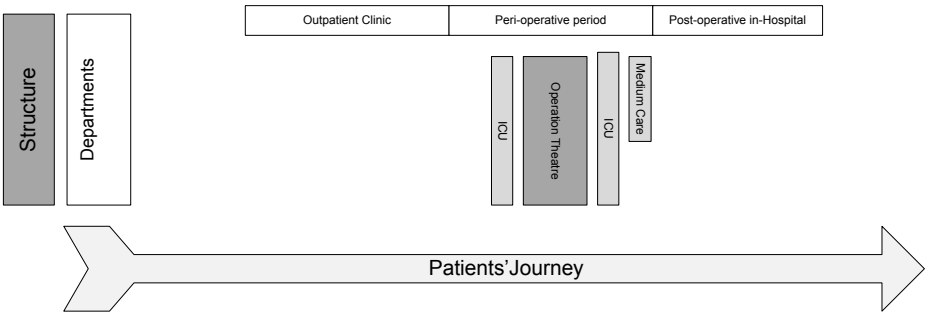
Following implementation of pre-operative optimization, 68 patients were compared to 32 patients operated prior to implementation. Optimization started one day before the esophagectomy in the ICU. A $ScvO_2$ <70% was treated with fluids and inotropics according to protocol.

Results

Sepsis occurred in 4% of optimized and 25% of control patients (p=0.004), anastomic leakage occurred in 12% of optimized patients and 25% of control patients (p=0.14). Optimized patients were less likely to be re-admitted to the ICU (p=0.07) and had a shorter median in-hospital–LOS of 10 [9-15] vs 16 [13-35] days (p<0.001). A targeted $ScvO_2$>70% was achieved in 77% of the optimized patients, in the optimized group delta $ScvO_2$ increased with 4 [0-7]%. Patients not reaching the target $ScvO_2$ were more likely to have a cardiovascular medical history (73% vs 37% p<0.02).

Conclusion

In this observational evaluation study targeted on preoperative $ScvO_2$-guided optimisation of patients treated with an open transhiatal oesophagectomy, we observed an association with a shorter in-hospital length of stay and less infectious complications. These results suggest that preoperative optimisation could be beneficial in this specific group of high-risk surgical patients.



Introduction

Worldwide an estimated 400,000 patients per year are diagnosed with oesophageal cancer with a 5 years mortality rate of up to 80% [1,2]. In the Netherlands 2000 patients per year are diagnosed with oesohageal cancer and this number is increasing. While adjuvant chemo-radiation therapy has improved the overall prognosis, patients are assumed more vulnerable to peri-operative complications, although this was not confirmed in the CROSS trial [3]. Open transhiatal esophagectomy for invasive or high grade dysplasia has been associated with substantial postoperative morbidity such as pulmonary edema, pneumonia, anastomotic leakage and mortality. For example, anastomotic leakage occurs in up to one-fourth of the patients and is associated with prolonged hospital length of stay and mortality [4].

It is increasingly recognized that the peri-operative care of patients undergoing major surgery affects outcome [5-6]. Predominantly, pre-operative optimization of hemodynamics is thought to improve postoperative outcome, but the exact mechanism of action remains unclear. Putative beneficial effects may include improved wound healing and less infectious complications related to an improvement in hemodynamics and better tissue perfusion. Conversively, aiming for a higher cardiac output might result in a more pronounced tendency for bleeding and cardiopulmonary complications.

The ambiguous results of pre-operative optimization in unselected high-risk surgical patients is possibly related to the heterogeneity of the patients included [10-15], while effects in specific patient groups have not been reported. The majority of patients undergoing major abdominal surgery, present themselves with functional intravascular volume deficit [16]. Apart from pre-operative fasting, anesthesia, and mechanical ventilation, inadequate intake in patients and the effect of neo-adjuvant chemo-radiation therapy imply that this patient group might be most likely to suffer from hypovolemia. For this reason we selected patients with oesophageal cancer for pre-operative optimization.

In view of the limited knowledge of how optimization influences outcome [17] and the assumption that pre-operative optimization may exert both beneficial and deleterious effects on postoperative complications and outcomes in high risk surgical procedures, we studied the association between optimization and a comprehensive set of complications. We hypothesized that a higher $ScvO_2$ and cardiac output as a result of pre-operative optimization, would result in less morbidity, specifically related to improved wound healing and infection. On the other hand, per-operative blood loss might be negatively influenced in the optimized group with a higher cardiac output. Therefore, intra-operative blood loss and the need for blood products were also monitored.

We prospectively evaluated these items with the implementation of $ScvO_2$-derived pre-operative optimization in patients undergoing transhiatal oesophagectomy. Beforehand we decided to compare data from optimized patients with patients operated without preoperative optimization from the preceding 2 years prior to this change in policy. In addition, within the group of optimized patients, we determined the differences in outcome between patients who did achieve their $ScvO_2$ target and patients who did not. The primary outcome of this observational evaluation, study was length of stay in-hospital as an overall outcome measure of changes in morbidity. Infectious complications, amount of per-operative blood loss, use of blood products, duration of mechanical ventilation, postoperative start of enteric feeding, incidence of re-intubations, ICU re-admission, ICU length of stay (ICU-LOS), and in-hospital mortality were secondary endpoints.

Methods

Patients and study design

All successive patients with $T_{1-3}N_{1-2}M_0$ distal (below Z line) oesophageal cancer and cardiacarcinoma with extension into the oesophagus are treated with neo-adjuvant chemoradiation according to the CROSS trial [3] followed by transhiatal oesophagectomy with gastric tube reconstruction and cervical anastomosis. In our hospital this is the preferred surgical procedure for oesophageal cancer. Patients with more proximal located oesophageal tumours and patients who had an intra-thoracic anastomosis for limited cardiac cancers, were not included in this study. In this group of patients no laparoscopic procedures were performed during the study period. Acute resection was an exclusion criterium. All patients received a jejunostomy for enteric feeding, starting within 24 hours after surgery. Pre-operative chemo-radiation was part of the treatment according to the CROSS trial and implemented as standard procedure for all patients in 2009. All patients were operated by the same surgeon (JJB) in the Radboud University Medical Center Nijmegen.

In this before/after observational evaluation study, the outcome of patients treated according to the pre-optimization protocol was compared with a control group operated in the 2 years prior to implementation. This two year prior period was chosen because most changes in ICU treatment, like e.g. low tidal volume ventilation, SDD in the years before, had been established as common practice. The operating surgeon had performed over 100 procedures before the chosen control period. Half-way 2011 a clinical pathway for patients treated for oesophageal cancer including pre-operative optimization and aspects of the "Enhanced recovery program in colorectal surgery" together with standardized intra-operative care and a clinical pathway for the surgical ward after discharge from the ICU was implemented.

The study was carried out in accordance with the Dutch Guidelines for the review of research ethics committees and informed consent. Since this was a retrospective cohort study and no additional information was gathered that was burdensome to the patients, the medical ethical committee MEC of region Arnhem-Nijmegen waived the need for informed consent. Data-analysis was performed anonymously after de-identification of the patient records.

Optimized cohort

Patients were admitted to the intensive care unit (ICU) one day prior to surgery. In the ICU, patients received an arterial line (radial artery) and a central venous catheter was introduced in the right subclavian or right jugular vein. As a surrogate of cardiac output, we determined intermittently the central venous oxygen saturation ($ScvO_2$). Similarly as

in several other peri-operative optimization studies [18-19]. Fluid challenges and inotropics were administered according to the intervention flow chart (figure 1). In case of (a history of) atrial fibrillation or when sinus tachycardia was observed, milrinone, instead of dobutamine, was administered (figure 1). In order to facilitate perfusion and oxygenation in the gastric tube anastomoses, ketanserin as vasodlilator up to 2 mg/hour was administered until ICU discharge, when the mean arterial blood pressure was above 65 mmHg[20]. To further investigate the effects of optimization within the intervention group, we compared patients that achieved the predefined goals to those that did not.

Control cohort of non-optimized patients

In this control cohort, all patients were pre-operatively admitted to the surgical ward (with oral access to fluids and food, but no intravenous fluids) and postoperatively transferred to the ICU for postoperative treatment and monitoring.

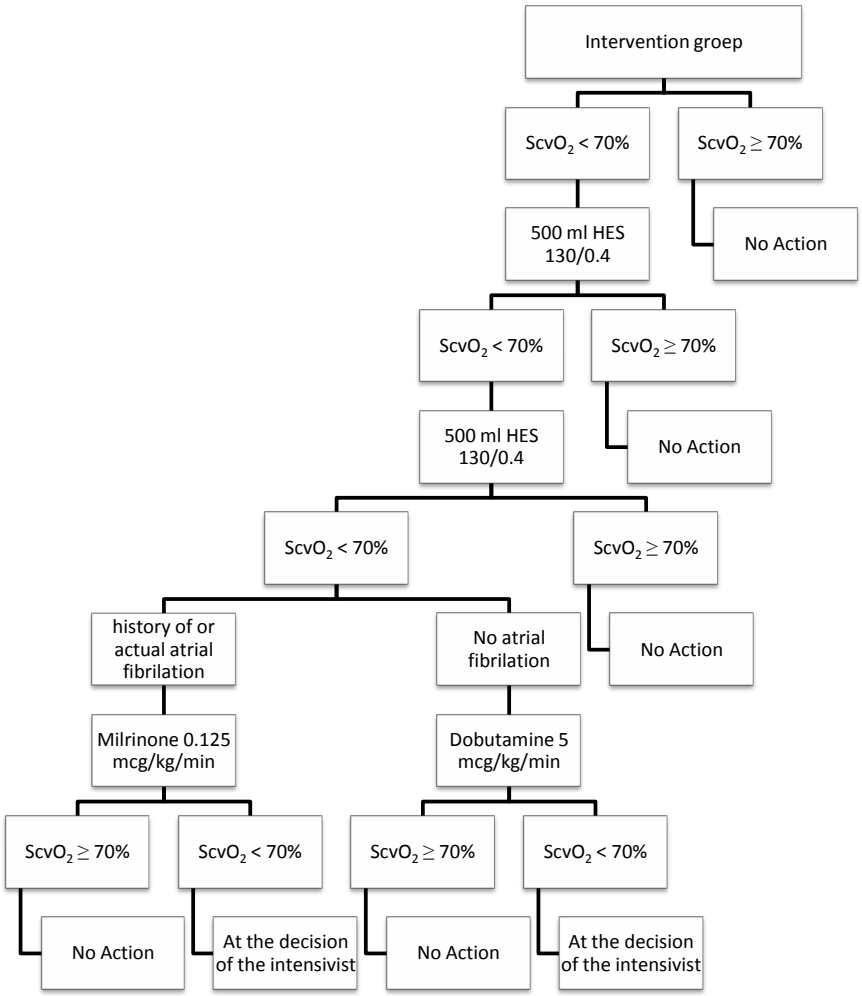
Pre and postoperative protocol

Indications for pre-operative nutrition or antibiotics did not change during the study period. Selective bowel decontamination and low tidal volume ventilation are part of the standard procedures in the ICU and did not differ between the patient groups. Although since 2004 'Enhanced Recovery Program' in colorectal Surgery is a standardized procedure in the departments of surgery and anesthesiology resulting in a restrictive volume policy during abdominal colorectal surgery, this program was not implemented for oesophagectomy patients during the study period [21]. Blood transfusion triggers did not change during this period. Furthermore, per- and postoperative pain treatment with ropivacaine and sufentanyl via an epidural catheter was administered according to the same protocol in both groups. A patient centered analgesic pump was added if the patient was able to use this. ICU-discharge criteria did not change during the entire study period. Intra and post operative protocol was not ScvO2 guided and the same per-operative protocol for anesthesists and postoperative ICU protocol was used in both groups. Pulse, mean arterial pressure >65 mmHg and diureses > 0.5 ml/kg/hour were the main goals for treatment.

End-points of the study

The primary outcome of this study was length of stay in-hospital as an overall outcome measure of changes in morbidity. Infectious complications, amount of per-operative blood loss, use of blood products, duration of mechanical ventilation, postoperative start of enteric feeding, incidence of re-intubations, ICU re-admission, ICU length of stay (ICU-LOS), and in-hospital mortality were secondary endpoints.

Figure 1: Haemodynamic treatment algorithm intervention group.



Statistics

Because of the relatively small sample size, normal distribution of data could not be assumed and all continuous variables are reported as median and interquartile range [IQR] and tested with Mann-Whitney U. Differences in dichotomous variables were analyzed with Chi-square test. Analysis of covariance (ANCOVA) was used with log-transformed continues outcome variables and dichotomous outcome variables were used for logistic regression analysis.

Because of the explorative nature of this study and to increase the sensitivity to detect differences between groups, adjusting for multiple testing was performed.

All statistical analyses were performed using SPSS version 20.01 for windows (IBM, SPSS statistics, Chicago, IL, USA). A p-value <0.05 was considered to indicate statistical significance.

Results

Pre-operative phase

The optimized group consisted of 68 consecutive patients and the non-optimized group of 32 consecutive patients. In the intervention group 87% of the patients were treated for adenocarcinoma comparable to 77% in the control group (p=0.3). There was no significant difference in TNM classification between the two groups (table 1, p=0.7). Patients in the optimized group tended to be older, were more likely to use anticoagulant therapy and more additional nutrition was started in the pre-operative outpatient period. In the control group patients consulted the dietician pre-operative in the outpatient clinic when weight loss was more than 5 % or oral enteral feeding was not possible. During these years the policy changed in a standardized referral to the dietician by the surgeon. Additional nutrition was prescribed as carbohydrate and protein enriched oral drinks, 4 patients received parenteral nutrition during one week. Pre-operative immuno-nutrition was not part of the nutritional support. For unknown reasons, patients in the intervention group appeared less likely to have used antibiotics pre-operatively,. More patients suffered from chronic pulmonary diseases in the optimized group. Other baseline characteristics were comparable between groups (table 1).

$ScvO_2$ was ≥ 70% in 32 (47%) patients at baseline. Hemodynamic optimization resulted in a significant increase in $ScvO_2$ of a median of 4.0 [0-7.0]% from 70 [66-73] to 73 [71-77]%. Target $ScvO_2$>70% was achieved in 49 (77%) of the patients. Maximum heart in the optimized group was lower during the ICU stay 93 [79-105] vs 98 [95-113], p=0.02 .

Minimum Systolic blood pressure during ICU stay was higher in the intervention group 107 [93-119] vs 92 [81-111], p=0.02. In the group of pre-operative optimized patients a median of 1415 [IQR 904-1993] ml fluids was administered pre-operatively and 9% of the patients received inotropics. The control group was not monitored pre-operatively, did not receive inotropics or i.v. fluids, but had free oral access to fluids and food (table 1).

Table 1: Demographic and preoperative characteristics.

	Control group (n=32)	Intervention group (n=68)	Differences (*p-value)*
Age in years	60 [53-64]	63 [57-69]	*0.08*
Male (n, %)	26 (81%)	58 (85%)	*0.77*
BMI kg/m^2	25 [22-27]	26 [24-28]	*0.14*
APACHE-II score *	14 [10-16]	10 [8-12] *	*0.002*
Baseline $ScvO_2$ (%)	n.a.	70 [66-73]	*n.a.*
Preoperative chronic comorbidity (n,%)			
Diabetes mellitus	6 (19%)	11(16%)	*0.78*
Pulmonary disease	1 (3%)	15 (22%)	*0.02*
Cardiac vascular disease	9 (28%)	29 (43%)	*0.19*
Preoperative medication			
Preoperative iv fluid (ml)	Free oral access, no iv fluids	1415 [904-1993]	*n.a.*
Preoperative inotropics	0(0%)	6(8.8%)	*0.17*
Beta blocker (n,%)	7 (22%)	18 (27%)	*0.80*
Oral anticoagulant therapy (n,%)	2 (6%)	19 (28%)	*0.02*
Additional nutrition (n,%)	2 (6%)	23 (34%)	*0.003*
Antibiotics (n,%)	4 (13%)	0 (0%)	*0.02*
Neoadjuvant chemoradiation (n,%)	17 (53%)	48 (71%)	*0.62*

Data are expressed as median and interquartile range [IQR] unless otherwise stated.
* APACHE-II score was measured postoperatively on the ICU in the control group, and was preoperatively measured in the intervention group due to the preoperative optimisation on the ICU. BMI = body mass index; IV = intravenous; n.a. = not available

Peroperative phase

The duration of operation was not significantly different between groups (table 2). Patients in the optimized group received less fluids during the operation (median 2750 [2150-3500] vs 4000 [2900-5250] ml; p<0.001) and were more likely treated with vasopressors compared with the control group (88% vs 41%; p<0.0001). The use of fluids was at the discretion of the attending anaesthesiologist who did not have information on the preoperative fluid balance. Although more patients in the optimized group used anti-coagulants (p=0.02), blood loss was less (median 600 [450-900] vs 910 [600-2000] ml; p=0.002), and the volume of blood products administrated was lower compared to the control group (median 275 [275-519 vs 600 [300- 1200] ml; p=0.001). The number of patients that

needed blood products was also less in the optimization group compared to the control group (6% vs 34%; p<0.001, table 2). Extubation of the patients was at the discretion of the attending anaesthesiologist a the end of the procedure. If the patient was not extubated after surgery the attending intensivist decided when the patient could be extubated according to the existing extubation protocol.

Table 2: Intraoperative characteristics and postoperative results.

	Control group (n=32)	Pre-optimised group (n=68)	Differences (*p-value*)*
Operation duration (min)	169 [144-183]	184 [159-208]	*0.04*
Blood loss during operation (ml)	910 [600-2000]	600 [450-900]	*0.002*
Administration of blood products			
- Number of patients (n,%)	11 (34%)	4 (6%)	*0.03*
- Blood product administered (ml)	600 [300-1200]	275 [275-519]	*0.001*
Haemoglobin (mmol/l) level at time of transfusion	5.1 [4.7-5.8]	4.8 [4.5-5.3]	*0.21*
Intraoperative vasopressors (n,%)	13(41%)	60 (88%)	*<0.0001*
Intraoperative inotropics (n,%)	5 (16%)	10 (19%)	*0.58*
Total of administered fluid (ml)	4000 [2900-5250]	2750 [2150-3500]	*<0.0001*
POSTOPERATIVE RESULTS			
Complications (n,%):			•
• Pulmonary	• 15 (47%)	• 32 (47%)	• *1.0*
• Empyema	• 2 (6%)	• 5 (7%)	• *1.0*
• Cardiovascular	• 5 (16%)	• 18 (27%)	• *0.31*
• Superficial wound infection	• 7 (22%)	• 6 (9%)	• *0.11*
• Anastomotic leakage	• 8 (25%)	• 8 (12%)	• *0.14*
• Stenosis anastomose	• 8 (25%)	• 20 (29%)	• *0.81*
• Re-laparotomy	• 6 (19%)	• 5 (7%)	• *0.17*
• Mediastinitis	• 3 (9%)	• 1 (2%)	• *0.09*
• Pleural oedema	• 12 (38%)	• 29 (43%)	• *1.0*
• Sepsis	• 5 (16%)	• 3 (4%)	• *0.004*
Re-intubation (n,%)	5 (16%)	6 (9%)	*0.32*
Epidural dysfunction (n %)	7 (22%)	14 (21%)	*1.0*
Additional analgesics (n,%)	9 (28%)	31 (46%)	*0.04*
Total fluid balance (ml) at discharge ICU in ml	3010 [1632-4362]	1810 [545-3190]	*0.03*
Duration of mechanical ventilation in hours	8.0 [3.5-23.7]	5.2 [3.7-7.5]	*0.04*
Start of postoperative enteric nutrition (hours)	7.0 [1.4-29]	3.4 [1.0-21]	*0.13*
Re-admission ICU (n,%)	8 (25%)	6 (9%)	*0.06*
LOS ICU in days	2 [1-7]	2 [2-3]	*0.72*
LOS in-hospital in days	16 [13-35]	10 [9-15]	*<0.0001*
Mortality in hospital (n,%)	3 (9%)	0 (0%)	*0.01*

Data are expressed as median and interquartile range [IQR] unless otherwise stated.
* Log-transformed continues outcome variables were tested using ANCOVA and dichotomous outcome variables were tested using logistic regression analysis, both adjusted for lung problems and use of anticoagulant therapy.
LOS = length of stay

Postoperative phase

Although the optimized patients were admitted to the ICU one day prior to surgery (according to protocol), their total ICU-LOS was similar to the control group (table 2). Patients in the optimization group needed less fluids postoperatively, and had a significantly less positive total fluid balance (median 1810 [545-3190] vs 3010 [1632-4362] ml; p=0.03) at ICU discharge. The incidence of sepsis was significantly lower (4% vs 25%; p=0.004). No difference was found between the two groups according to anastomotic leakage, but in the optimized group all patients with a leakage (12%) had Type I leakage, localized in the cervical area. Two patients within the control group had Type II leakage, one patient had dissemination of infected effusion in the pleural cavity and one patients had an abdominal sepsis because of leakage of the jejunostomy because of enteral feeding impaction. Optimized patients were extubated sooner (median 5.2 [3.7-7.5] vs 8.0 [3.5-23.7] hrs; p=0.04), less likely to be re-admitted to the ICU (10% vs 25%; p=0.07), and their hospital length of stay was shorter 10 [9-15] vs 16 [13-35] days (p<0.0001). Three patients (9%) in the control group died (two with sepsis and one with cardiac complications), while none of the patients died in the optimized group (p=0.03). No other differences were found between both groups.

Relation between achieved $ScvO_2$ and outcome

Due to protocol violation, no preoperative $ScvO_2$ was measured in 4 patients during the pre-optimization phase. In total, 49 (77%) patients achieved the target $ScvO_2$. Patients with a history of cardiovascular disease were more likely not to achieve a $Scv0_2$ >70% compared to optimized patients with no history of cardiovascular disease (p<0.01), (table 3). Preoperative fluid administration was similar in patients that achieved the $ScvO_2$ target (median 1440 [907-1998] ml), compared to patients who did not reach the target $ScvO_2$ (median 1287 [790-2165] ml). In total 6 (9%) optimized patients were treated with inotropics, of which 4 patients did show an increase of $ScvO_2$ (from 64 % to 69 %), but did not reach the target $ScvO_2$. No differences in outcomes were found between patients who achieved the $ScvO_2$ target or a rise of delta $ScvO_2$ of more than 4% and who did not (table 3).

Table 3. Differences in characteristics and outcome related to achieved and increase in $ScvO_2$

	$ScvO_2$ ≤70% (n=15)	$ScvO_2$ >70% (n=49)	*Differences (p-value)*	$\Delta ScvO_2$ ≤ 4 % (n=32)	$\Delta ScvO_2$ >4% (n=31)	*Differences (p-value)*
Age in years, median [IQR]	67 [58-71]	61 [56-69]	*0.21*	60 [52-69]	65 [59-69]	*0.13*
Gender male (n, %)	13 (87)	41 (84)	*0.78*	25 (78)	29 (94)	*0.08*
APACHE-II score, median [IQR]	11 [7-11]	10 [8-13]	*0.58*	10 [6.8-11.2]	10 [8-13]	*0.37*
Diabetes mellitus (n,%)	5 (33)	6 (12)	*0.06*	3 (9)	8 (26)	*0.09*
Pulmonary disease (n,%)	4 (27)	9 (18)	*0.49*	5 (16)	8 (26)	*0.32*
Cardiovascular disease (n,%)	11 (73)	18 (37)	*0.01*	12 (38)	17 (55)	*0.17*
Beta-blockade (n,%)	9 (60)	9 (18)	*0.02*	9 (28)	9 (29)	*0.93*

Oral anticoagulant therapy (n,%)	9 (60)	10 (20)	*0.03*	7 (22)	12 (38)	*0.15*
Total fluid given ml. preoperative, median [IQR]	1287 [790-2165]	1440 [907-1998]	*0.73*	1396 [996-1787]	1561 [787-2090]	*0.51*
Fluid balance (ml) preoperative, median [IQR]	620 [222-945]	420 [-400-775]	*0.28*	471 [222-795]	680 [-125-1105]	*0.52*
OUTCOME *						
Anastomotic leakage (n,%)	1 (7)	7 (14)	*0.44*	3 (9)	5 (16)	*0.42*
Wound infection (n,%)	1 (7)	4 (8)	*0.85*	4 (13)	1 (3)	*0.17*
Sepsis (n,%)	0 (0)	3 (6)	*0.33*	2 (6)	1 (3)	*0.57*
Fluid balance in ml at discharge ICU, median [IQR]	970 [216-3745]	1943 [1128-3333]	*0.36*	1830 [545-3745]	1410 [530-3070]	*0.54*
Re-admission (n,%)	2 (13)	5 (10)	*0.73*	5 (16)	2 (7)	*0.25*
LOS-ICU (n,%)	2 [2-4]	2 [2-2]	*0.87*	2 [2-2]	2 [2-3]	*0.52*
LOS-in hospital (n,%)	10 [8-17]	10 [9-14]	*0.65*	10 [9-15]	10 [9-15]	*0.66*

IQR = interquartile range; LOS = length of stay

Discussion

In this before/after study we evaluated the association between pre-operative hemodynamic optimization and the occurrence of predefined complications and outcome in transhiatal esophagectomy patients related to their duration of hospitalization as the primary endpoint measure. The in-hospital length of stay was significantly less in pre-operatively optimized patients. We observed that hemodynamic optimization was associated with a significant reduction in the occurrence of sepsis. Mechanical ventilation time was reduced and while optimized patients were admitted to the ICU one day earlier, total ICU-LOS was not different between the two groups. No deleterious effects related to a higher cardiac output were observed in the optimized patients. In contrast, hemodynamic optimization was associated with less per-operative blood loss and a reduction in the use of blood products, even though more patients used anticoagulant medication. Finally, we observed a reduction in the ICU readmission rate and mortality rate.

We postulated, in accordance with a meta- analysis [22], that a positive effect of hemodynamic optimization could be achieved best when organ failure, tissue perfusion defects, or infectious complications had not yet occurred, especially in patients with a considerable mortality risk. Optimization of the $ScvO_2$ in the pre-operative and postoperative period to a level above 70%, was demonstrated to reduce the number of complications and length of hospital stay in a heterogeneous group of high risk surgical patients [18,23,24]. While patients with oesophageal cancer are more likely to be volume depleted, the effects of pre-operative optimization with a $ScvO_2$ target above 70% has not been investigated in this specific group of patients. As fluid administration is a cornerstone in pre-operative optimization, it remains important to realize that fluid therapy may be considered a two-edged sword, as a too liberal fluid policy may exert deleterious effects [25,26]. The enhanced recovery after surgery program aims to avoid peri-operative volume overload. Restrictive fluid therapy is thought to result in less intestinal edema and enhanced recovery. Importantly, our study confirms previous reports [19,27,28] that pre-operative optimization, including fluids and inotropics, results in a lower need for fluids during and following surgery. We do not have an explanation for the use of more vasopressors following the intervention. The anesthesists had no knowledge of the amount of fluids that had been given to the patients in the ICU, excluding that they were more likely to administer a vasopressor because of that.

Although some differences in outcome between the optimized and control group were clinically significant and suggest that pre-operative hemodynamic optimization through better tissue perfusion results in less infectious complications, this association is less straightforward than it might appear. For example, within the optimized group of patients

we found no differences in outcome between patients who achieved the target of $ScvO_2$ >70%, compared with those who did not. Moreover, no differences were detected between the patients with an increase in $ScvO_2$ more than 4%, compared to less than 4%. This suggests that a $ScvO_2$ above 70% or an increase in $ScvO_2$ by itself may not be beneficial per se. In other words, these results could indicate that pre-operative optimization is beneficial for patients undergoing esophagectomy, but may not be directly related to reaching a $ScvO_2$ >70%. A similar phenomenon was also observed in a study using a lactate clearance driven protocol in sepsis patients. The interventions aimed to improve lactate clearance in sepsis patients resulted in a better outcome, while the decrease in lactate concentration was similar compared to the control group [29]. Taken together, these results suggest that interventions aimed to improve the hemodynamic condition may exert beneficial effects. The chosen marker (either SvO_2 in our study or lactate in the sepsis study) however, may not adequately reflect the improvement of the patient's condition. For example we did not look at microcirculation or inflammatory response in the intervention group, which could both have a role in the improvement of the patients in the optimized group.

Several other limitations of our study need to be addressed. First and most relevant, the study design introduces many opportunities for bias, as this is a non-matched pre-post design cohort study even though data in the intervention group were collected prospectively. Although no other differences in treatment protocol occurred during the study period, we cannot exclude that medical or organizational interventions, unknown to us, did affect our results. During the same period changes in treatment in different patient groups were observed which were not part of any protocol or implementation strategy which could have affected the results of this study. Because the treatment of our patient group has a pathway through many departments, half-way 2011 a clinical pathway for patients treated for oesophageal cancer was implemented. This clinical pathway combines pre-operative optimization in the outpatient clinic, the ICU and aspects of the "fast track" surgery protocols based on the "Enhanced recovery program in colorectal surgery (ERAS)" together with standardized intra-operative care and a clinical pathway for the surgical ward after discharge from the ICU.

Also, patients were not randomized and several differences in baseline characteristics were present between the two groups. The influence of additional nutrition (more patients in intervention group) and antibiotics (more patients in control group) are difficult to determine. Adherence and non-adherence to the existing protocols could have been different due to education or individual pre-occupation. More patients in the intervention group used anticoagulant therapy, but still blood loss and need for blood products was less in this group. Also, other differences, apart from the preoperative optimization were present, e.g., use of vasopressor therapy during the operation, that may have influenced

the end points of the study. The enhanced recovery program for colorectal surgery with emphasis on prevention of fluid overload and use of vasopressors during surgery was implemented before our optimization study in oesophageal cancer patients started. This may have influenced the peroperative treatment choices of the anaesthesiologist and could have resulted in the use of early or more vasopressors. The central line in situ could have lowered the incentive for the anaesthesiology team to measure $ScvO_2$ and treat low peroperative values even when mean arterial pressure was sufficient with vasopressors. Nevertheless, this is the first study examining the effect of optimization within a specific group of high-risk surgical patients and the results related to infectious and bleeding complications are in line with the observed effects of outcome measures in this specific group. Differences in ICU treatment, surgeons protocol adherence in different centres would introduce confounding factors and bias as well and due to the small number of eligible patients per centre, a randomized controlled trial is unlikely to be conducted for this specific group of patients. In this observational evaluation study targeted on preoperative $ScvO_2$-guided optimization of patients treated with an open transhiatal esophagectomy we observed an association with a shorter in-hospital length of stay and less infectious complications, shorter mechanical ventilation time, and lower mortality. Blood loss and use of blood products was less, not more, in patients that received preoperative hemodynamic optimization. These results suggest that preoperative optimization could be beneficial in this specific group of high risk surgical patients. Nevertheless, a clear relationship between achievement of target $ScvO_2$ and clinical outcome could not be established. Because of this, it is difficult to make clear cut recommendations for current daily practice.

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Implementation and evaluation of a Clinical Pathway for pancreaticoduodenectomy procedures: a prospective cohort study

Marion van der Kolk, Mark van den Boogaard, Femke Becking-Verhaar, Hettie Custers, Hans van der Hoeven, Peter Pickkers, Cees van Laarhoven.

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Abstract

Introduction

Medical and nursing protocols in perioperative care for pancreaticoduodenectomy are mainly mono-disciplinary, limiting their integration and transparency in a continuous healthcare system. The aim of this study was to evaluate adherence to a multidisciplinary clinical pathway for all pancreaticoduodenectomy patients during their entire hospital stay and to determine if the use of this clinical pathway is associated with beneficial effects on clinical end-points.

Materials and Methods

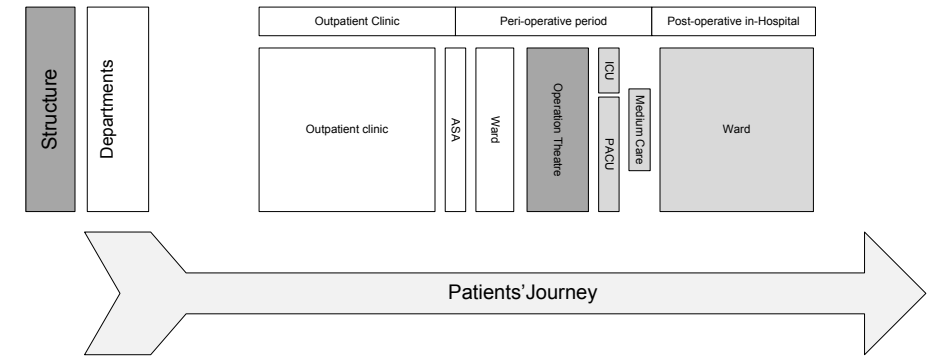
A prospective cohort study was conducted in 95 pancreaticoduodenectomy patients treated according to a clinical pathway, including a variance report, compared to a historical control group (n=52) with a traditional treatment regime.

Results

Process evaluation of the clinical pathway group revealed that protocol adherence throughout all units was above 80%. Major complications according to Clavien-Dindo Classification grade ≥ 3, decreased from 27% to 13%; p=0.02. Hospital length of stay was significantly shorter in the CP group, median 10 days [IQR: 8-15], compared with the control group, median 13 days [IQR: 10-18]; p=0.02.

Conclusion

The use of a clinical pathway in pancreaticoduodenectomy patients was associated with high protocol adherence, improved outcome and shorter hospital length of stay. Variance report analysis and protocol adherence with a Prepare-Act-Reflect-Cycle are essential in surveillance of outcome.



Introduction

Pancreaticoduodenectomy for pancreas tumours and periampullary tumours is considered high-risk surgery and is associated with high morbidity (30-70%), and a mortality of 1-5% in specialized centres (1,2). Centralization of pancreas surgery and advances in surgical techniques resulted in more patients being operated for advanced staged tumors (40, 60). Patients with more co-morbidity receiving pre-operative chemotherapy and/or vascular reconstructions in advanced disease, need more complex perioperative care. Currently this is facilitated by multiple guidelines, and medical and nursing protocols. This complexity demands an overall multidisciplinary approach and clear communication.

Different departments are involved in the treatment during the patients' journey through the surgical ward, operation theatre, Post Anesthesia Care Unit (PACU) and Intensive Care Unit (ICU). However, large differences in the actual use of these protocols are present between the different units and medical and nursing staff members (5,6). Moreover, while multidisciplinary teamwork for these patients is essential, the development and implementation of a clinical pathway (CP) involves many aspects of the total patient care and should therefore be multidisciplinary by doctors and nurses as well.

A clinical pathway may facilitate the care for this group of high-risk surgery patients by unifying different protocols into one multidisciplinary protocol for all units, the patient will visit during the hospital stay. This may result in an increased protocol adherence, less morbidity and improved outcome. Key elements of a CP are guidelines, evidence based clinical protocols and best practice rules, together with a coordinated sequence of activities of the multidisciplinary team (7). Registration, monitoring and evaluation of adherences, variances and outcomes are part of a CP and can be part of a process driven pathway (8).

A multidisciplinary CP has therefore many evaluation moments and scheduled actions. To keep the patient on the 'pathway', the CP mandates a registered response of the nurse or doctor if results are outside the range of the prescribed boundaries.

Many CPs have been developed for high volume with low-risk and with average-risk health care procedures in order to reduce complications (9-12). The postoperative phase of the patient spent in the ICU or PACU however, are seldom part of a CP (13). A clinical pathway including the PACU/ICU stay, mandates an hour-to-hour care plan during the post-operative stay in the ICU/PACU (14). Many standardized care plans related to a pancreaticoduodenectomy have been published, focussing on the use of an enhanced recovery program after surgery (ERAS) with elements like early mobilization, early enteral feeding, pain treatment and reduction of iv-fluid administrations to shorten the length of hospital stay (15-19). In these care plans, a reduction of hospital length of stay (LOS), morbidity or mortality was not always observed. Crucially, the ICU period of these patients was not integrated in these protocols.

The aim of this study was first to determine the feasibility to develop and implement a multidisciplinary CP including a variance report for all pancreaticoduodenectomy patients during their entire hospital stay. Second, to determine if the use of this CP is associated with an improvement of patient's morbidity and outcome.

Methods

Setting and patients

The Radboud University Medical Center in Nijmegen is a 1000 bed university hospital, including a 32 beds closed format ICU, a 5 beds PACU, and a 30 beds gastro-intestinal (GI) oncology surgical ward. An anaesthesiologist with a resident are supervising the PACU. The ICU is supervised by the intensivists, with intensivists-in-training, and residents. They all work in close relation with the surgical team. On the surgical ward, nurses, physician assistants and young residents are caring for patients undergoing a pancreaticoduodenectomy, under daily supervision of the senior GI-oncology medical staff. Since the centralization in 2012 of pancreas surgery in the Netherlands, approximately 80 pancreas operations (60 malignant cases) are operated annually in the Radboudumc. As a result, the logistics and perioperative care of our pancreatic surgical program needed reflection and rescheduling.

Development of the Clinical Pathway

The development of the multidisciplinary CP for pancreaticoduodenectomy was a multistep procedure with the use of lessons learned from the development and implementation

of the cardiac and esophageal CP's, previously developed in Radboudumc, and started in 2013.

The first step was redefining and searching for evidence underneath the surgical, anaesthesiology and intensive care unit protocols in the perioperative period. This was a multidisciplinary procedure, undertaken by the physician assistants, senior nurses, 'key' nurses and medical staff (20-27). Instead of a traditional "day-to-day-care" plan for the surgical ward, an "hour-to-hour" care plan had to be developed, including the PACU and ICU care. It was important to identify potential barriers and facilitators in these settings, in order to tailor the implementation strategy (28-31). An evidence based implementation strategy according to Grol was used (32). Second, a unique variance report ('Radboud variance report'; Appendix 1) had to be incorporated and developed together with the CP (33). This Radboud model of variance report enables nurses, physician assistants and young residents to execute predefined actions in accordance with and within the preset boundaries of a variance protocol, without having to wait for approval of the responsible physician first (Dutch law and order for health care professionals BWBR0006251 chapter IV, article 35).

Until 2012, a surgical pancreas matrix for (peri)operative care was used at the surgical ward. The historical control group was treated according to this matrix including the surgical medical and nursing protocols without the variance report. In the PACU and ICU these patients were treated according to different PACU and ICU protocols. This pancreas matrix, was used as backbone for further multidisciplinary development of the CP. As part of the development and implementation strategy a small group of 'key' nurses responsible for other CP's reflected on the concepts of the pancreas CP and variance report as part of a Prepare-Act-Reflect Cycle (P-A-R-cycle).

The pancreas CP had to be a continuum from admission to discharge from the hospital. Essential elements included: restrictive intra-operative fluid use, strict pain control, early mobilization, early drain and tube removal, and early enteral feeding. Post-operatively, early warning scores (EWS) are measured at least once during every 8 hour shift or more frequent,whenever indicated by the nurses, with strict directives for action by nurses according to the variance report (34).

Patients with a malnutrition universal screening tool (MUST) score above 2, need an active feeding intervention according to the quality system of health care in the Netherlands. We decided that patients with a MUST above 2 should start with total parenteral nutrition (TPN) within 24 hours after surgery. Publications on calorie deficit and enteral feeding or TPN after surgery in ICU patients, often do not take in to account malnutrition and MUST

score >2. Our protocol prescribes that if the gastric tube can be removed, the patient need to start with oral/enteral feeding, and TPN need to stop as soon as the oral intake of the patient is above 1000 kcal. (22, 23, 35-38). TPN should be started on day 3 if patients had a MUST score of 1 and enteral feeding had not been started on day 3. All patients with a gastroparesis without signs of sepsis or ileus on day 7 will be given a naso-jejunal tube by the gastroenterologist through the gastro-jejunostomy and start enteral feeding (39). In contrast to ERAS based protocols, deviations from the CP had to lead into prompt actions according to the variance report.

Implementation of the Clinical Pathway

After informative meetings for medical and nursing staffs, including reflections on the positive aspects of previous CPs, bedside training started on the surgical ward and PACU/ICU in 2014. Implementation of the pancreas CP would introduce an essential change in daily practice for most nurses, physician assistants and medical staff. The first step in teaching was getting acquainted to the CP vision that would result to one continuous multidisciplinary protocol (32). In nursing and medical staff meetings updates of the project were discussed, and feedback was welcomed by the CP developers. During this teaching period, especially new PACU specific aspects arose for the pancreas CP, including new variance report criteria, and as an interactive process of PAR cycles, these criteria were incorporated in the pancreas CP during the development. In this try-out period, feedback was asked and given every four weeks during the multidisciplinary team meetings of the project. After 4 months of teaching and try-out period, it was concluded that it was feasible and safe to use the pancreas CP with the Radboudmodel variance report for patients during their entire clinical stay, including the PACU/ICU. With the completion of this implementation step, the pancreas CP was considered being implemented and our study on the use of the CP and variance report for all pancreaticoduodenectomy patients started on the first of September 2014, 18 months after the start of the development of the CP, including many PAR cycles. Patients treated for other pancreas procedures than pancreaticoduodenectomy were considered candidates to have the benefits of the pancreas CP during their stay in PACU/ICU and ward, but were not included in this study. Protocol adherence was measured per pathway action. We considered protocol adherence if a deviation from the CP resulted in the correct action, according to the CP, or if no action was needed and no action was started. No protocol adherence was defined as: wrong actions or no actions if actions were needed. Deviations from the CP had to be described in the variance report or patient record.

Design

This is a pre-post design study. After the implementation of the pancreas CP, patients treated according to the CP were compared with a historical control group of patients treated with standard perioperative care for pancreaticoduodenectomy according to the original pancreas matrix and monodisciplinary protocols and operated between 2009-2012.

End-points

Primary endpoint was to determine the feasibility and safety, including incidence of post-operative complications, according to Clavien-Dindo classification, of the use the CP (40). Secondary endpoints were in length of stay (LOS) in-hospital, postoperative fluid balance, gastroparesis, protocol adherence to mobilization, drain removal, radiologic and surgical re-interventions, ICU readmission, hospital readmission and mortality rate.

Statistics

Continuous variables were described as median and inter quartile range [IQR] and tested with the Mann-Whitney U test. Differences in dichotomous variables were analyzed using Chi-square test. Due to the exploratory nature of this study, and to increase the sensitivity to detect differences between groups, no correction for multiple testing was performed. With our convenience sample size of 95 patients in the CP-group and 52 patients in the control-group, our study had 80% power to demonstrate a 7% absolute reduction of post-operative complications. All statistical analyses were performed using SPSS version 20.01 for windows (IBM, SPSS statistics, Chicago, IL, USA).

Results

Development results of the Clinical Pathway

Nurses, physiotherapists, dieticians and medical staff specialized in pancreas surgery contributed to the development of the pancreas CP and the variance report. This resulted in a set up of clear and safe boundaries in taking clinical treatment decisions and an up scaling system to consultation with a key-nurse or senior staff members, if actions according to the variance report did not seem right.

First, the pancreas CP for medical and nursing decisions was written according to existing evidence based protocols, best practices and guidelines. Finally, a multidisciplinary variance report was incorporated (Appendix table 1: summary of the differences between clinical pathway and control surgery and Appendices 2-3: variance report).

For the analysis of the developmental process we evaluated barriers and facilitators for protocol adherence. For this, interviews and questionnaires were used, focussing on possible barriers and facilitators for protocol adherence to the new CP. An important facilitator was the motivation of nursing and medical staff to ask for guidance and training in the use of this protocol. The most important barrier was that using the protocols was experienced as a time consuming processes of getting acquainted with the system, resulting in feelings of loss of autonomy for doctors and nurses. Key-nurses together with medical leadership were essential for awareness, feedback and motivation during development, implementation and the use of the CP.

Implementation results of the Clinical Pathway

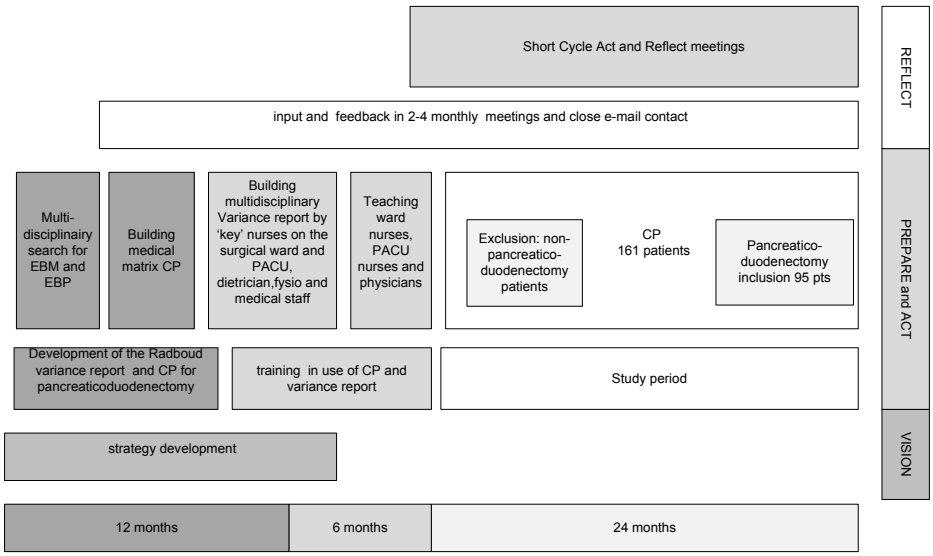
First, the medical aspects of the CP were implemented on the ward followed by the nursing aspects. Because the lack of experience with CPs, the care providers working on the PACU received more time for training and bedside teaching and started later with implementation. Key-nurses at the surgical ward gave guidance and were partner for the key-nurses of the PACU.

Evaluation after the implementation process was performed every 2 months during the first 6 months, and after this period whenever needed. These evaluations resulted mostly in questions or new ideas for a change in the CP from the units or when less compliance was observed. The variance report was an important tool for evaluating compliance. When compliance of one of the CP domains was below 80%, feedback was given by the key-nurse or surgeon through focussed teaching sessions for nurses and residents.

After a period of 18 months the pancreas CP was implemented and evaluation of protocol adherence was 80% for PACU/ICU periods and 60% for the surgical ward. The latter was mainly influenced by a low compliance to drain removal (<50%). According to the pancreas CP, drain removal was allowed if amylase level in the drain was below 500 U/L and volume below 200 ml/day. Deviations turned out to be primarily a system problem of postponing drain removal during weekends. After recognition of this system problem an active policy started and protocol adherence on this item improved to above 80%.

Following the implementation, in September 2014, the outcome study of the pancreas CP was started (Figure 1 implementation flow chart).

Figure 1: implementation of pancreas CP and study flowchart.



Clinical outcomes

Between September 2014 and September 2016, in total 95 elective consecutive pancreaticoduodenectomy patients were treated within the pancreas CP. Semi-acute pancreaticoduodenectomies (for bleeding tumours) and other types of resections (e.g. total pancreatic resections or pancreaticoduodenectomies with resection of a secondary colo-rectal tumor) were no part of the study. A cohort of 52 consecutive elective pancreaticoduodenectomy patients treated before the CP implementation period between 2009 and 2012 was identified as historical control group. Their perioperative treatment

had been according to the underlying matrix protocol that was used as base for the development of the CP. Three surgeons in the pre-CP period operated the pancreaticoduodenectomy patients. Results between these surgeons did not differ,and perioperative care was regulated by protocols. These surgeons were also responsible for pancreas surgery in the clinical pathway period.

Baseline characteristics between the two groups were not significantly different, apart from a higher number of CP patients receiving Portal vein resection or Celiac trunk/ Superior Mesenteric Artery (SMA) vessel exploration (table 1).

Table 1: Baseline characteristics of pancreas CP and control groups of pancreaticoduodenectomy.

	Clinical Pathway N=95	Control N=52	*P*
Age, median [IQR]	66 [57-72]	66 [58-72]	0.98
Male, n (%)	56 (58.9)	35 (67.3)	0.26
Stent/ (PTC) percutaneous drainage, n (%)	59 (61.5)	28 (53.8)	0.34
Pulmonary comorbidity, n (%)	13 (13.7)	4 (7.7)	0.52
Cardial comorbidity, n (%)	13 (13.7)	10 (19.2)	0.62
Vascular comorbidity, n (%)	29 (30.5)	16 (30.8)	0.80
Diabetes, n (%)	21 (22.1)	16 (31.4)	0.4
Preoperative chemotherapy, n (%)	4 (4.2)	0	
Portal vein resection, n (%)	20 (21.1)	1 (1.9)	<0.001
Celiac trunk/ SMA exploration, n (%)	6 (6.3)	0	

Legends: IQR = First and Third Inter Quartile Range, PTC = Percutaneous Transhepatic Cholangiography, SMA = Superior Mesenteric Artery

Intra-operative data

The median intra-operative amount of fluids administered was 3900 ml [IQR 3000-4600] in the CP patients versus 5200 ml [IQR 4000-6000] in the control group (p<0.001). Post-operative fluid balance and fluid balance on day 1 postoperative were also significantly lower in the CP group versus the control group (p<0.001; table 2). Although more portal vein resections and Celiac trunk and explorations along the superior mesenteric artery were performed, blood loss was less in the CP patients: 755 ml [IQR 500-1100] versus 1303 ml [IQR 656-2402] (p<0.001, table 2).

Post-operative data

Adherence of pain and hemodynamic interventions according to the variance report was 100% at the PACU/ICU, and a step up approach regarding pain control was adequately used according to CP protocol. Hemodynamic interventions in accordance with the variance report was not needed and not started in 17% of the CP patients, and 57% of the

CP patients needed an extra hemodynamic intervention which was subsequently started according to CP protocol. In total 26% of the patients were treated with vasopressors on arrival in the PACU/ICU which could be reduced during their stay. Significantly more CP patients were swing mobilized within 24 hours compared with the control group,respectively 83% versus 19%, p=0.001. Especially poor pain control and patients' feelings of weakness, early after the operation, were recorded as reasons not to start swing or mobilization at the surgical ward. Trigger for complications was the EWS, in 32% of the patients in the CP group the EWS was above 3. Interventions on a high EWS were adequate and according to the variance report > 95% of the patients.

Table 2: Intra-operative results of pancreas CP and control groups of pancreaticoduodenectomy.

Fluid and vasopressor management	Clinical pathway N=95	Control N=52	*P*
Intra-operative fluids in ml, median [IQR]	3900 [3000-4600]	5200 [4000-6000]	<0.001
Fluid balance, at the end of the procedure, median [IQR]	405 [-107-833]	1926 [1253-2818]	<0.001
Intra-operative blood loss, median [IQR]	755 [500-1100]	1303 [656-2402]	<0.001
Intra-operative vasopressor use, n (%)	94 (99)	48 (92)	0.22

Considering clinical outcome, major complications according to the Clavien-Dindo Classification grade 3 or more occurred less frequently (13% vs 27%, p=0.02) in the CP group, compared to the control group (51). One patient had a Clavien-Dindo 4b complication as a result of pancreatic leakage complicated by sepsis with EWS >6 on day 7 and hemorrhagic bleeding on day 14 in the CP group. This complication was successfully treated by radiologic coiling of the gastroduodenal arteria and splenic artery.

Less patients suffered from gastroparesis grade B and C in the CP group compared to the control group 9% versus 62 %, p<0.001, as were radiologic interventions: 11 % versus 27 %, p=0.04. In the control group the gastric tube was not removed when production was reduced but was left in place and blocked and could be removed if after measurement of retention after 8 and 16 hours being was less than 100 ml per 8 hours. Pancreatic leakage and chylus leakage, readmission to ICU and readmission to hospital did not significantly differ between the CP group and control group. Median times to drains removal were also not influenced. The mortality rate was low and not different between groups (table 3).

Table 3: Postoperative data of pancreas CP and control groups of pancreaticoduodenectomy.

	Clinical pathway N=95	Control N=52	*P*
Postoperative PACU, n (%)	81 (85)	29 (55)	0.002
Mobilization swing, according to protocol (within 24 hours) n (%)	78 (83)	10 (19)	0.02
Mobilization out of bed in days, median [IQR]	2 [1-2]	2 [2-3.3]	0.001
Gastroparesis (ISGPS): n (%)			
• Type A	20 (21)	15 (29)	<0.001
• Type B	7 (7)	18 (35)	
• Type C	2 (2)	14 (27)	
Pancreas leakage, n (%)	12 (13)	5 (10)	0.82
Drain in situ, days, median [IQR]	6 [4-10]	7 [5-12]	ns
Clavien Dindo Classification n (%)			
3a	9 (10)	9 (19)	0.02
3b	1 (1)	4 (8)	
4b	1 (1)	0	
5	1(1)	0	
Radiologic reïntervention, n (%)	10 (11)	14 (27)	0.04
Relaparotomy, n (%)	3 (3)	4 (8)	0.01
Readmission ICU, n (%)	7 (7]	7 (14)	ns
Readmission Hospital, n (%)	12 (13)	9 (18)	ns
LOS in hospital, days, median [IQR]	10 [8-15]	13 [10-18]	0.02
30-days mortality, n (%)	1 (1)	0 (0)	ns
90-days mortality, n (%)	2 (2)	1 (2)	

Discussion

This study illustrates that development of a CP for pancreaticoduodenectomy is an iterative multidisciplinary process, starting with a dynamic protocol with improvements through Prepare-Act-Reflect cycle evaluation and change moments. Implementation of the pancreas CP in all units involved in the entire (peri-) operative process (OR, PACU/ ICU/ surgical ward) took 18 months. Process evaluation of the prospective CP group revealed that protocol adherence, was successfully achieved in >80% for most of the criteria throughout the clinical stay. Comparison of both cohort groups on main clinical outcomes showed that major complications according to the Clavien-Dindo Classification grade 3 or more and hospital LOS in the CP group was significantly lower compared to the control group. In addition, implementation of the CP was associated with a reduction of gastroparesis, an improved post-operative fluid balance and patients in the CP-group were more likely to receive early mobilization and adequate actions on EWS above 3. These data illustrate that implementation of a CP in this specific group of patients is feasible, safe and likely to be beneficial for the patient.

Analyzing reasons not to follow the variance report was part of this study. Human factors were often reasons for deviation from the report. For example, insecurity of young professionals on decisions leading to postponing gastric tube removal. The prevention of gastroparesis is part of a very active P-A-R-cycle in the CP. Nurses, young doctors and patients want to prevent discomfort for the awake patient while re-positioning of the tube, even if early removal is according to protocol. The action was a team reflection on the discomfort of a needless gastric tube for too long and as a result, delay in starting early oral nutrition and well being.

Postponing early mobilization because of patients' pain or weakness did occur. In all situations the iterative process of repeated and specific education was important to explain the reasons behind the CP and guidance.

Considering the diverse landscape of clinical pathways and surgical care plans, it is difficult to compare the different studies. In studies, related to implementation of clinical pathways, not all hospital wards involved in the clinical process (like PACU/ICU) were included, which negatively influences the continuous care process for the patient. Also different treatment regimes make reliable comparison and evaluation of different CP's difficult. Regarding the available studies we found only studies not covering the whole clinical stay, excluding parts of the post-operative period. Also usually merely some specific aspects like ERAS, drain and gastric tube removal were addressed (18). A standardized care plan for pancreaticoduodenectomy patients was retrospectively studied in another study focussing on predictors of LOS in-hospital (15). Specific ERAS pathways, without PACU/ICU periods involved, focussed on in hospital LOS, outcome mortality and morbidity. While these were unchanged, measurement of protocol adherence was not part of the study (16). Braga et al. evaluated the compliance to the enhanced recovery protocol and concluded patients with low compliance had a higher incidence of complications (41).

Our results are in pursuance of previous studies that showed that a CP or standardised care plan for pancreaticoduodenectomy patients resulted in an earlier start of solid enteral feeding and a shorter hospital LOS and less readmissions. Importantly, protocol adherence to predefined targets has not been part of these studies as was analysis of the reasons not following the protocol and its association to outcome.

Comparing our study to these studies, a similar effect on reduction of complications, hospital LOS, readmissions, gastroparesis, time to enteral feeding and time to mobilization was found. Our present study also illustrates that it is feasible to implement a CP that covers the entire clinical admission, applying different targets of the various involved units (e.g. focus on hemodynamic and respiratory vital parameters at the PACU/ICU, versus focus

on EWS and ERAS criteria at the surgical ward). Nurses were also able to start adequate therapy in accordance with the variance rapport when early warning scores deviated from the target. Moreover, new to the other studies is that this study, via the variance report method, exposed the barriers and facilitators of CP adherence. In addition, these two monthly formal meetings to evaluate variance report deviations and their barriers and facilitators, enabled us to discriminate the difference of loss of compliance to a protocol due to complicated discourse of operations, versus loss of professional adherence to the CP protocol.

The current study has several limitations. Most importantly, this is a single-centre pre-post-intervention study. The intensity and duration to develop the CP, as well as the implementation process limit the feasibility of using other study designs. In addition, the historical group was not formally matched, which together with the fact that no randomisation was carried out, induces a higher risk of confounding factors. No relevant differences in patient characteristics between the different study periods were observed. However, the case load per surgeon increased which could be considered as a possible confounding factor. We considered the development of a CP as the most appropriate intervention to re-schedule the process. Prospective complication registration was part of the daily supervised perioperative care as well as the discharge procedure in both groups. Moreover the prospective database on outcome and complications of the control group (2009-2012) served as a document to identify barriers and facilitators for building the clinical pathway. Furthermore, no relevant changes in other procedures, staffing levels, technical infrastructure or other major changes that could influence patient management occurred and during the whole study period there were no changes in interventions that are known to influence morbidity or mortality in the ICU such as strict glucose regulation, early goal-directed therapy, use of corticosteroids, prone positioning and low tidal volume ventilation. Second, no a priori power calculation was carried out, implying that the risk for a type 1 or 2 error has not been overcome. Using our convenience sample, we did calculate that our study has 80% power to demonstrate a 7% change in complication rate, while we observed that the complication rate halved. Nevertheless, the sample size of the study and the discussed design issues should make us aware of the possible overestimation of the outcome differences. In contrast, this does not necessarily apply for the process analysis part. As no comparison of the CP group was made to the control group, the conclusions of the process analysis merely indicate that CP development, implementation and high level of adherence to such a CP, throughout all units involved in the perioperative process is feasible within a relative short period and up to a high standard.

Lessons learned

This study shows us, in line with the implementation of our cardiac surgery CP and esophageal surgery CP (42), that it is feasible to develop and implement a CP for pancreaticoduodenectomy procedures for all involved units like the PACU/ICU and surgical ward through the entire clinical perioperative period. In all units the CP targets need to be aligned and the use of a variance report discriminates complications-related to failure of professional adherence. Implementation is an iterative process that takes time to become comfortable in use for all involved units. Key-nurses together with medical leadership were essential for awareness, feedback and motivation during development, implementation and the use of the CP.

Future perspectives

In order to overcome the methodological drawbacks of this study and to validate the CP methods, a multicenter stepped-wedged cluster randomised controlled trial would be ideal. However, due to the complexity of the implementation and intervention with barrier and facilitator analysis in different hospitals and units, interpretation of the results will be difficult. Exploring the validity of similar CP's is in line with the need for quality assurance of standardised treatment regimes with high protocol adherences.

For the near future, continuous monitoring, wearables, electronical medical data recording with pop-up facilities warning medical and nursing staff for deviations from the clinical pathway, will likely be of help in building more complex pathways. Possibly, patients with high co-morbidity will be able to follow their personalized clinical pathway with the help of dedicated staff.

Conclusion

The use of the CP was associated with a reduction of perioperative morbidity. Essential new tools include a variance report analysis, scheduled barrier and facilitator analyses, and the iterative PAR cycle protocol development, performed by a multidisciplinary team. Development, implementation and use of a CP throughout the hospital stay for patients undergoing pancreaticoduodenectomy is a multistep procedure in which we showed that this is feasible and safe.

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Appendix

Table 1 : Similarities and differences between clinical pathway and control period

Clinical pathway	Control
Outpatient clinic	
Tumour Board Treatment Advice (PACON)	Tumour Board Treatment Advice (PACON)
Oral and written patient information	Oral patient information
Dietician contact: MUST screening tool, nutrition advice and if needed supplemental feeding oral or enteral.	Dietician contact if needed supplemental feeding oral or enteral
Frailty screening tool	
Medication Verification	
Training advice : Home trainer use, 1 hour walking per day	
Surgical ward	
Use of ERAS protocol	Use of ERAS protocol
Preoperative Lanreotide ®	Preoperative Lanreotide ®
Thrombosis prophylaxis Nadroparine® 5700 E	Thrombosis prophylaxis Nadroparine® 2850 E
6:00 day of operation : last Preop® or clear liquid intake, anti-thrombosis compression stockings.	
Pain management and control according to protocol together with Pain Service Team	Pain management together with Pain Service Team
Early Warning Score once per 8 hours and whenever indicated together with actions by nurses	Early Warning Score once per 8 hours and whenever indicated action by resident
Patient communication between doctors, nurses and handover situations according to Reason, Story, Vital Signs, Plan (RSVP)	Patient communication between doctors, nurses and handover situations not specified
Mobilisation after surgery: swing and out of bed within 24 hours	Mobilisation after surgery: swing and out of bed within 24 hours
Gastric tube: if production < 200 ml in 12 hours remove of tube	Gastric tube: if production is reduced, start clamp tube and remove if retention is < 100 ml in 8 hours (after two consecutive periods of 8 hours)
Drain removal if production < 200 ml and amylase < 500 U/L per day	Drain removal if amylase < 500 U/L per day and operating surgeon agrees
Nutrition : MUST > 2 start TPN on day 1 postoperative	Nutrition: enteral feeding will start on day 1 if the patient has a jejunostomy. Oral fluids according to ERAS
MUST = 1: if gastric tube has not been removed on day 3 start TPN	If no enteral intake is possible on day 6 start TPN has to start on day 7
All patients: if the gastric tube cannot be removed because of gastroparesis on day 7 without signs of sepsis or ileus: placement of an jejunal tube through the gastro-jejunostomy by the gastroenterologist and start enteral feeding	
Glucose control	Glucose control
Discharge Criteria Use of the variance report if actions are not according to protocol.	Discharge Criteria not specified

Table 1 : Continued

Clinical pathway	Control
Operating room	
Use of ERAS protocol	Use of ERAS protocol
Pain control by Epidural Catheter	Pain control by Epidural Catheter
Central venous line in the vena jugularis, if indicated PiCCO	
Antibiotic prophylaxis 15-60 min pre-incision. Cephazolin® and Metronidazol®. If a stent or percutaneous transhepatic drain has been placed in the ductus Choledochus use Piperacilline/Tazobactam as prophylaxis.	Antibiotic prophylaxis 15-60 min pre-incision. Cephazolin® and Metronidazol®. Otherwise if indicated by the surgeon
Target postoperative fluid balance between 0 and 500 ml	Postoperative fluid balance not specified but according to ERAS
Handover to PACU personal by surgeon and anaesthesiologist according to RSVP	Handover to PACU personal by anaesthesiologist
PACU/ICU	
Entrance in PACU: every 15 min: RR and heart rate control until stable, than every 30 min RR and pulse	Entrance in PACU: Every 15 min: RR and pulse control until stable than every 30 min RR and pulse
Continuation of Antibiotics will be part of the sign out procedure after surgery	Continuation of Antibiotics at the decision of the surgeon
Normothermia (>36.0 degree Celsius), bearhugger or heating system if necessary	Normothermia (>36.0 degree Celsius), bearhugger or heating system if necessary
Every hour (1st until 24th hour): Respiratory status after extubation: saturation, respiratory frequency, coughing and deep breathing exercises Hemodynamics: heart rhythm, heart frequency, RR, $ScvO_2$ (if indicated). Excretions: urine, drain, gastric tube	Every hour (1st un till 24th hour): Respiratory status after extubation: saturation, respiratory frequency, coughing and deep breathing exercises Hemodynamics: heart rhythm, heart frequency, RR, $ScvO_2$ (if indicated). Excretions: urine, drain, gastric tube
Temperature	Temperature
Pain and sedation: NRS pain score	Pain and sedation: NRS pain score
RASS and CAM ICU	RASS
Mean arterial Pressure (MAP) between 70 mmHg and 100 mmHg and heart frequency between 60 and 90 per minute. Different targets than the CP prescribes possible after approval of the supervising anaesthesiologist .	Mean arterial Pressure (MAP) targets need approval of the supervising anesthesiologist.
MAP should be above 70 mmHg : if below start norepinefrine.	
i.v. fluids: ERAS protocol Balance between 0 and + 500 ml /24 hours	
Urine production has to be above 0.5 ml/kg/hour. Protocol "oliguria PACU"	Urine production has to be above 0.5 ml/kg/hour. Protocol "oliguria PACU"
First choice of inotropics: dobutamine	First choice of inotropics: supervising anesthesiologist
Stress-ulcer prophylaxis Pantoprazol® 1 dd 40 mg iv/po	Stress-ulcer prophylaxis Pantoprazol® 1 dd 40 mg iv/po

Table 1 : Continued

Clinical pathway	Control
PACU/ICU (Continued)	
Nausea and Vomiting: 3/day 4 mg ondansetron® iv (Maximum until 36 hours after surgery) 3/day metoclopromide 3/day 10 mg iv (3/day 5 mg iv when kidney function reduced) (cave QT time)	Nausea and Vomiting: If indicated : 3/day 4 mg ondansetron ® iv If indicated : 3/day metoclopromide 3 day 10 mg iv (3/day 5 mg iv when kidney function reduced) (cave QT time)
Anti -thrombosis prophylaxis Nadroparine 5700IE	Anti -thrombosis prophylaxis Nadroparine 2850 IE
Mobilization according to protocol: starts within 24-hours	
Gastric tube: See CP surgical ward	Gastric tube
Drain: 2 abdominal drains Drain production control every hour : aspect and volume, 100-200 ml/hours. If production >200 ml/ hours or >400 ml/4 hours contact surgeon	Drain: 2 abdominal drains Drain production control every hour : aspect and volume, 100-200 ml/hours. If production >200 ml/ hours or >400 ml/4 hours contact surgeon
Electrolyte control and interventions	Electrolyte control and interventions
Glucose regulation: normoglycaemia (glucose 5.0-10.0 mmol/l)	Glucoseregulation: normoglycaemia (glucose 5.0-10.0 mmol/l)
Discharge criteria: handover procedure according to RSVP, vital signs accepted by the surgical ward.	Discharge criteria according to PACU
Use of the variance report if actions are not according to protocol.	

Mini review: Clinical pathways in high-risk surgery: What makes them special and why do we need them?

B.M. van der Kolk, M.W.A.M van den Boogaard, C.J.H.M. van Laarhoven

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Introduction

Peri-operative management in high-risk surgery is confused by many clinical algorithms, protocols, guidelines and decision making rules (1). Clinical Pathways (CP) were developed in the 1990s to integrate these different nursing and medical protocols in multidisciplinary care plans for low- and intermediate-risk surgery. Originally they were designed to balance the quality of care and costs by focussing on better use of resources, a maximum quality of care and minimization of delay in diagnosis and treatment(2,3). Development and successful implementation of a CP for high-risk surgery may improve the quality of care as well, potentially reducing serious complications and improving Patient Reported Outcome.

The "European Pathway Association" states, that a CP is a method for patient-care management of a well-defined group of patients during a well-defined period of time. A clinical pathway explicitly states the goals and key elements of care based on Evidence Based Medicine (EBM) guidelines, best practice and patient expectations by facilitating the communication, coordinating roles and sequencing the activities of the multidisciplinary care team, patients and their relatives (2).

Modern high-risk surgery where the patient will visit many departments, including the intensive care unit, demands a multidisciplinary approach. Surgical specialists are no longer capable nor in charge of the entire clinical process. Communication and exchange of information during the treatment of the high-risk surgical patient depends on various specialists like anesthesiologists, intensive care specialists and consultants from e.g. endocrinology and nephrology. During the clinical patients' journey various departments (with many different caregivers), such as the surgical ward, operating theatre, Post Anaesthesia Care Unit (PACU) and Intensive Care Unit (ICU), are involved in treating high-risk surgical patients. At present, these units have their own protocols, guidelines and key-performance indicators in most hospitals. Apart from content differences on same topics (e.g. trombosis prophylaxis) in these monodisciplinary protocols, there are also large differences in the actual use of and compliance to these protocols, which are presently causing large treatment variation both among medical and nursing staff care-givers. These differences in use are often unnoticed by the caregivers in the care process the patient receives, and Prepare-Act-Reflect (P-A-R) cycles are seldom properly implemented.

Evidence from literature

The use of CPs has been discussed in the literature for more than two decades and the definition has become blurred. Pro and con discussions about using CPs are often the result of fear that the use of a CP becomes a business model, or that pathway companies will build CPs that are not aligned to the work process of the departments in a hospital. As a

result, Work-as-imagined (WAI) designed by experts and built into guidelines, will differ from Work-as-Done(3). The difference will be based on interpretation of EBM and best practice guidelines, resources and fear of loss of autonomy of care-givers that peri-operative care will become the result of a cooking class with only one chef, (4, 5).

The method of analysis of a complex process intervention as a CP is still subject of discussion (6, 7). However, looking in more detail at the literature, although reports are still scarce, the evidence of favourable outcome due to CPs is becoming stronger and new research will be added in the near future. (8, 9).

Many CPs have been developed for predictable trajectories, where clinical interventions must be given in a timely manner, and this implies that a CP is often a day-to-day care plan for a specific disease or medical procedure (10). So far, many CPs have been developed for high volume, low- and average-risk healthcare procedures to reduce variations in care, complications, length of stay (LOS) or costs (11-14). Clinical pathways with the aim to standardize care and to reduce variation in care and outcome are also well known in e.g. cardiology and pulmonology. CPs in cardiology, with focus on management of acute coronary syndromes and reduction of time-to-stent or time-to-surgery, did show an improve of protocol adherence and an improved outcome (15-17). An international multicenter cluster randomized controlled trial in 22 hospitals, with the aim to reduce 6-month readmission rate after COPD exacerbation, showed a significant reduction in the 30-day readmission rate without a reduction in 6-month readmissions. Evidence-based key interventions were better performed after implementation of a CP compared to usual care (18). CPs in day-care surgery, hip surgery, hysterectomy and colorectal surgery show reductions in postoperative morbidity and LOS (19). Furthermore, multimodality strategies like ERAS programmes (enhanced recovery after surgery) are nowadays the core interventions in many CPs for middle- and high-risk surgical procedures like colorectal and pancreatic surgery (20, 21). Unfortunately, these CPs, including the ERAS programme, lack the complete spectrum of all clinical aspects during the entire clinical stay of the patient, as well as the multidisciplinary approach needed in high-risk surgery. These limitations may be responsible for unclear outcome benefits of CPs and ERAS (9).

A process intervention like the development and implementation of a CP for high-risk surgery could potentially reduce serious complications and LOS. Today, many complex CPs in high-risk surgery do not include the ICU period in their CP. In most CPs in the ICU, only aspects of ICU care are implemented in care bundles, such as mechanical ventilation, the treatment of sepsis and septic shock, analgesia or treatment of pneumonia (22-31). Unfortunately, CP literature describing the total clinical journey of the high-risk surgical patient, including the ICU period, is not available.

Clinical pathway development and implementation processes

Three essential phases can be identified before a dynamic and sustainable CP is properly in use,: the development, implementation and maintenance (working) phase.

Essentially, in developing a CP, a multidisciplinary team of doctors and nurses, with clear clinical leadership, assimilates different monodisciplinary protocols and guidelines to one overall multidisciplinary CP. Analysis of barriers and facilitators at the different units should be part of the development and implementation strategy. P-A-R cycles performed by key-nurses and key-doctors have to be part of this iterative process of pathway implementation and use, and are essential for a dynamic CP. These cycles will inform users about the actual use and need for readjustment of protocols based on changes in the underlining evidence or best practice guidelines. Communication between the different units, for alignment of treatment during the clinical stay, is key to a successful development and implementation of a multidisciplinary CP. Whereas the PACU/ICU mandate an hour-to-hour care plan for the initial postoperative period, the post-operative surgical wards need a day-to-day care plan. Hemodynamic, respiratory and adequate pain control criteria are essential during these intra- and early post-operative periods. Criteria such as hand-over guidelines, early warning scores, pain assessment, feeding and mobilization protocols are essential ingredients, becoming more important when the patient is transferred to the surgical ward.

To complete development and strengthen the compliance process a variance report overarching both the pre-operative, intra-operative (anaesthesia) and all post-operative periods should, ideally, be incorporated into the CP. With such variance reports, deviations from the CP are recognised and interventions, necessary to get back on the pathway, are instructed instantly. Variance reports thus enable nurses and young doctors to start treatment without waiting for time consuming approval from the consultant.

During implementation and maintenance phases P-A-R cycles are essential for dynamic improvement of the CP. Compliance measurements, derived from the variance report, are useful tools in PAR cycles for improvement. While working with the CP, and because the pathway is known to the patient and their families, their input can be integrated in the P-A-R cycle improvement by using Patient Reported Outcome Measures (PROM).

In the Radboud University Medical Center, we developed and implemented three multidisciplinary CPs in high risk surgical procedures for cardiac, esophagus and pancreatic surgery, which also included the PACU/ICU periods. The development of the CP for all cardiac surgery patients in this high-risk and high volume patient group acted as the blue print for the development of other low-volume, high-risk surgery related CPs in the intensive care.

The development and implementation phases were considered successful after achieving compliances to variance reports of at least 80%.

Evaluation of the clinical outcome of the CP in cardiac surgery patients resulted in more timely and better organized postoperative ICU treatment: improved blood pressure control, a more expedient adequate action to chest tube blood loss and faster weaning from mechanical ventilation (22). In CP cohorts of esophagus and pancreatic surgery a reduction in hospital LOS, as well as a significant reduction of major complications according to Clavien Dindo, was observed.

A successfully implemented CP in high-risk surgery can improve the quality of care, show a reduction in complications and will probably lead to a better Patient Reported Outcome and less waste of resources. New designs based on an iterative dynamic process for development and implementation, using variance reports with preset instructions, using barrier and facilitator analyses and P-A-R cycles, render systems with compliances > 80% and high levels of evidence of improved clinical outcomes. Essentially, all care-givers throughout the entire clinical process must be involved and aligned, as is the patient and their family, resulting in a Patient-centred-CP.

Conclusion

Although the concept of CPs goes back for more than two decades, a broad implementation of CPs in high-risk surgery which includes an ICU period has not been the subject of research in the past period to date. However, implementation of a CP including the ICU period in high-risk surgery has potential benefits and these benefits are not limited to cost-effectiveness. The potential for improvement in the clinical outcome can be tremendous.

Future perspective

To bring the development and clinical effectiveness of CPs to a higher level, new technologies can help in the development and implementation of CPs for the high-risk surgical patient. Patient data management systems (PDMS) have to be aligned to the dynamic CP. More complex pathways can be built with the use of continuous monitoring systems on surgical wards using validated digital wearables. Variance reports have to be built on trend analyses of continuous monitoring data derived from all units including operating theatre, PACU/ICU and surgical wards. Deviations from the pathway can be recognised sooner, resulting in early interventions to put the patient back on the pathway according to individualized preset goals. In this way CPs will empower nurses, physician assistants and residents in safe treatment decision making. Patients will experience more security during the treatment process and will be empowered by being able to follow their personalized clinical pathway. We assume that CPs can be an important tool and process intervention in patient safety and patient centred care.

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Summary

Summary

Clinical pathways, or care pathways (CPs), are developed to provide optimal care for a specific patient group and overcome unwanted differences of given care between individual patients and individual care-providers. Originally, CPs were designed to balance the quality of care and costs by focusing on better use of resources, aiming for optimal quality of care and minimization of delay in diagnosis and treatment. Development and implementation of clinical pathways are considered complex process interventions and are usually developed for predictable, non-complex procedures. We developed and implemented several CPs integrating nursing and medical protocols into multidisciplinary care plans for high-risk surgery patients in the intensive care unit (ICU). The content of the ICU related CPs does not just consist of multi-disciplinary or intra-disciplinary protocols and best practices, but is also a 'day-to-day' care plan describing all care, interventions or activities needed to be achieved within a specific period of time to provide optimal patient care. We hypothesized that a process intervention, like the development and implementation and use of a CP for high-risk surgery, may improve the quality of care, and will potentially lead to a reduction of serious complications. The CP is based on best practice rules, guidelines and evidence based medicine. In the ICU, a CP could be a uniform protocol together with an hour-to-hour schedule of interventions or actions on deviations for a specific group of patients. This schedule should focus on recognition of deviations from the pathway by nurses and should enable them to start treatment within the boundaries of prescribed variances. The development, implementation and evaluation of a CP in the ICU should be part of a Prepare-Act-Reflect cycle (P-A-R cycle), and should be dynamic to facilitate further improvements of care. Structure interventions in the system together with changes in guidelines (Work-as-Imagined, WAI) will effect Work-as-Done (WAD) relating to the CP, and all should result in agile adaptations.

The first part of this thesis will focus on the feasibility of the development and implementation of a postoperative hour-to-hour CP for cardiac surgery patients. We will also focus on trends over time after implementation of a CP in high volume, high-risk surgery. Analysis of facilitators and barriers within the structure or process are part of this thesis.

The second part of this thesis focuses on the development and implementation of CPs in low volume, high-risk surgical procedures such as pancreas surgery and esophageal surgery. We describe the use of a preoperative optimization protocol for open transhiatal esophagus resections in a closed-format ICU and the development and implementation of a CP for pancreaticoduodenectomy procedures from outpatient clinic to discharge after surgery. In both studies we did also analyze the effects relating to the outcome for the specific patient groups.

The development, implementation and evaluation of a postoperative CP together with a variance reportfor all cardiac surgery patients in the ICU is described in **Chapter 2**. The variance report enabled nurses to execute predefined actions in accordance with and within preset boundaries. The CP in this high-volume, high-risk patient group describes all multidisciplinary activities in the postoperative ICU process and primarily focuses on recognition of deviation from the pathway by nurses and their timely treatment within the boundaries of the prescribed variances. The aim of this study was firstly to develop and implement a CP for all cardiac surgery patients in the ICU, together with a unique variance report ('Radboud variance model'), describing all multidisciplinary activities in the ICU, and to achieve a protocol adherence above 80%. In addition, we analysed the results of protocol adherence in relation to outcome in the intervention group compared with a propensity matched historical control group treated according to the existing nursing and medical protocols in the year before the implementation of the CP. In a period of four months 84 consecutive CP patients were included and compared with 162 matched control patients admitted in the year before implementation. CP patients were more likely to receive timely and adequate treatment for derangements in electrolytes (96% vs 47%, $p<0.001$), blood pressure (90% vs 49%, $p<0.001$) and more timely treatment for chest tube blood loss (90% vs 10%, $p<0.001$). This study was not powered for differences in hospital and ICU length of stay, ICU readmission or mortality.

We demonstrated that it is feasible to implement a predominantly nurse-driven hour-to-hour CP in the ICU for cardiac surgery patients. In addition, the use of the CP for all cardiac surgery patients resulted in more timely and better organized postoperative ICU treatment. This included improved blood pressure control, electrolytes within range, temperature management, weaning from mechanical ventilation and more expedient action to chest tube blood loss. This implementation strategy and variance report developed in this high-volume, high-risk patient group served as a blue print for the development and implementation of a CP for low volume high-risk surgical procedures.

After implementation of a postoperative CP for cardiac surgery patients we studied trends and changes over time in the total group of over 7500 cardiac surgery patients treated in the nine years after the implementation of the CP. This study is described in **Chapter 3**. Primary aim of this study was to determine trends over time regarding inclusion and exclusion of patients in the CP. Patient characteristics were analyzed in three-year periods. Secondary aims included determining the trends over time and between groups in ICU and hospital LOS, re-operations, ICU readmissions, hospital mortality and 1-year mortality. Effects over time and clinical outcomes were determined within patients that were included in the CP, secondary excluded patients, or never included patients, as well as a subgroup analysis of patients with a high Log EuroSCORE >10. A retrospective

cohort study was performed in 7553 patients, operated between January 1st, 2007 and December 31st, 2015. The three identified patient groups were: patients treated according to the CP (n=6567), patients excluded from the CP within the first 48 hours after surgery (n=633), and patients that were never included in the CP (n=353). The implementation of the Patient Data Management System (PDMS) in 2013 was considered as a complex structure intervention, so we decided to analyse the effect of implementation of the PDMS as well, because we had the expectancy that the implementation of a new PDMS might have an impact on all processes regarding patient information, including care and safety. Following implementation of the CP in 2006, the percentage of patients treated according to the CP increased from 74% in the first year 2007 and stabilized at a percentage of 95% in 2012 to 2015. The median [IQR] Log EuroSCORE of patients treated according to the CP increased from 2.91 [1.54-5.71] to 3.30 [1.75-6.25] (p=0.016), indicating that over time care-givers are less reluctant to treat more complex patients according to the CP. Despite the fact that more patients with more comorbidities were included, the in-hospital LOS decreased from median 6 days [IQR 4-8] to 5 days [IQR 3-7] in the patients treated according to the CP (p<0.001). Overall, the in-hospital and 1-year mortality decreased from 1.5 to 1.1% and 3.7 to 2.9%, respectively (both p<0.05). Still, patients with a Log EuroSCORE >10 were more likely excluded from the CP (p<0.001). Patients with a Log EuroSCORE >10 treated according to the CP had a shorter ICU stay and in-hospital LOS compared to excluded patients with a Log EuroSCORE >10, (p<0.001). For more than one year following implementation of the PDMS, registration and correct tagging of patients according to their postoperative pathway was cumbersome. Nevertheless, implementation of the new PDMS did not influence the outcome data in the patient groups. In the subgroup analysis we observed that most high-risk patients were able to follow the CP. This continuous learning process in CP-guided care will lead us to more personalized pathways for high-risk patients and to shared decisions in person-centered care in the future. In addition, this study illustrates the sustainability following implementation of a CP in cardiac surgery patients over time. While more complex patients were treated according to the CP, clinical outcome improved. Needless to mention that other factors may also have contributed to better outcomes over these years.

In the **fourth chapter** we describe an observational evaluation study on preoperative central venous oxygen saturation ($ScvO_2$)-guided hemodynamic optimisation in a group of patients treated with an open transhiatal esophagectomy for carcinoma or high-grade dysplasia. Patients were admitted to the ICU for preoperative hemodynamic optimization. We studied the association between preoperative optimization and a comprehensive set of complications in 68 patients and compared this intervention group with a historical control group of 32 patients treated without preoperative optimization in the two years prior to the intervention. Our hypothesis was that preoperative optimization in a group

of low volume, high-risk surgical patients could result in less postoperative complications. Optimization started one day before the esophagectomy in the ICU. The matrix used for optimization enabled nurses and residents to start fluids and/or inotropic agents according to protocol if the $ScvO_2$ was below 70%. In the optimization group, median preoperative fluid infusion was 1415 ml [904-1993] and 8.8% of the optimized patients needed an inotropic to reach an $ScvO_2$>70%. A targeted $ScvO_2$>70% was achieved in 77% of the optimized patients. In the optimized group, delta $ScvO_2$ increased with 4 [0-7]%. Patients not reaching the target $ScvO_2$ were more likely to have a cardiovascular medical history (73% vs 37% p<0.02). Post-operatively, sepsis occurred in 4% of optimized and 16% of control patients (p=0.004), anastomic leakage occurred in 12% of optimized patients and 25% of control patients (p=0.14). Furthermore, optimized patients appeared less likely to be re-admitted to the ICU (p=0.07) and had a shorter in-hospital–length of stay of median 10 [IQR 9-15] vs median 16 [IQR 13-35] days (p<0.001). Mechanical ventilation time in the optimized group was median 5.2[IQR3,7-7,5] vs 8.0 [IQR 3.5-23.7] hours in the control group (p<0.03). There was no postoperative mortality in the optimized group, three patients died in the control group. We concluded that preoperative hemodynamic optimization was associated with shorter in-hospital length of stay, less infectious complications, shorter mechanical ventilation time and even lower mortality. Of interest, despite aiming for a higher cardiac output, blood loss and use of blood products was less in patients who received preoperative haemodynamic optimisation. These results suggest that preoperative optimisation could be beneficial in this specific group of high-risk surgical patients. Nevertheless, it should be emphasized that caution is warranted, as this was a single-center, pre-post intervention study.

The development and implementation of a CP in the ICU and in the Post Anesthesia Care Unit (PACU) for pancreatico-duodenectomy patients is described in **Chapter 5**. The pancreas CP was a continuum from hospital admission to hospital discharge. Essential elements of the CP included: restrictive intra-operative fluid use, strict pain control, early mobilization, early drain and gastric tube removal, and early enteral feeding all according to the Enhanced Recovery After Surgery (ERAS) protocol (Kehlet&Dahl, Lancet 2003). Early warning scores (EWS) were determined post-operative at least once during every 8 hour shift and whenever thought necessary by the nurses, with strict directives for action by nurses according to the variance report, both in the surgical ward, Post Anesthesia Care Unit and ICU. A prospective cohort study was conducted in 95 pancreaticoduodenectomy patients treated according to the CP, compared with a historical control group (n=52) with a traditional treatment regime. Primary endpoint was the incidence of post-operative complications, according to Clavien-Dindo classification (Dindo & Clavien, Annals of Surgery 2004). Secondary endpoints were, post-operative fluid balance, occurrence of gastroparesis, protocol adherence for mobilization, drain removal, radiologic and surgical

re-interventions, ICU readmission, in-hospital length of stay (LOS), hospital readmission and mortality rate. Process evaluation of the clinical pathway group revealed that protocol adherence throughout all components of the CP was above 80%. Major complications according to Clavien-Dindo Classification grade ≥3, was significantly lower in the CP group (13%) compared with the control group (27%); p=0.02. Hospital-LOS was significantly shorter in the CP group, median 10 days [IQR: 8-15], compared with the control group, median 13 days [IQR: 10-18]; p=0.02. The use of the CP was associated with a significant reduction of perioperative morbidity as reduction of gastroparesis (p<0.001) and less radiologic drainage interventions (p=0.04). Essential new tools included a variance report analysis, scheduled barrier and facilitator analyses, and the iterative P-A-R cycle protocol development, performed by a multidisciplinary team. We concluded that the development, implementation and use of a CP throughout the hospital stay for patients undergoing pancreaticoduodenectomy, is a multistep procedure which is feasible and safe.

In **Chapter 6** we reflect on the need for sustainable clinical pathways and the development of personalized care pathways in high-risk surgery**.** Although the concept of CPs goes back more than two decades, a broad implementation of CPs in high-risk surgery which includes an ICU period has not been the subject of research in the past period to date. Implementation of a CP, including the ICU period in high-risk surgery, has potential benefits and these benefits are not limited to cost-effectiveness. The chance to improve clinical outcomes is real. The European Pathway Association, e.g. on acute care, COPD and hip fractures, concluded that evidence-based key interventions are better performed after implementation of a CP compared to usual care. We argue that a successfully implemented CP will improve the quality of care, including a reduction of complications. It appears plausible that this will be related to improved patient reported outcome and more efficient use of resources. For successful implementation, all caregivers throughout the entire clinical process need to be involved and aligned, as well as the patients and their family. Augmented use of nursing potential is also paramount. Deviations from the pathway can be recognised more swiftly, resulting in more timely interventions to put the patient back on the pathway according to individualized preset goals. In this way, CPs will empower nurses, physician assistants and residents in safe treatment decision making. Patients will experience more security during the treatment process and will be empowered by being able to follow their personalized clinical pathway.

The general discussion and future perspectives are described in **Chapter 8,** with focus on the relationship between process interventions such as the development and implementation of clinical pathways and clinical outcome.

General discussion
and future perspectives

General discussion

Development and implementation of clinical pathways, or care pathways (CPs), are considered complex process interventions. In the 1990s CPs were developed to integrate nursing and medical protocols in multidisciplinary care plans, most often accomplished in predictable trajectories (1). In this thesis we describe the development and implementation of high-risk surgery related clinical pathways in the Intensive Care Unit (ICU). We focus on clinical pathways as a complex process intervention and a component of the Donabedian's trias: structure, process and outcome (2, 3). Development and implementation of a clinical pathway in the ICU in high-risk surgery is a multi-step procedure. The first step is the mutual decision of physicians and nurses to align protocols so that they can work uniformly, the second step is the multidisciplinary search for available evidence and best practice guidelines that have to be built into the future multidisciplinary CP. Following these two essential steps, the actual building of the CP can start. The method of implementation has to be part of the development of the multidisciplinary CP, before the implementation can finally start. During implementation of a standardized dynamic CP, the use of an associated Prepare-Act-Reflect (P-A-R) cycle with a purpose for continuous improvement is an essential aspect for a sustainable CP.

In this thesis we describe the development and implementation of high-risk surgery related CPs in the ICU and discuss steps we consider important for a successful CP development and implementation. We argue that adequate use of CPs can become a tool in the continuous improvement of quality of care, by the use of P-A-R cycles. Clinical outcome measurements together with P-A-R cycles of CPs may provide steering information and this can lead to transparency of given care. Research on outcome measures of CPs does have important limitations, mainly because of methodological issues.

Development of high-risk surgery related CPs in the Intensive Care Unit

For the development and implementation of the CPs in our hospital, nursing and medical protocols were reviewed and often redefined and, when available, based on Evidence Based Medicine (EBM), Evidence Based Practice (EBP) and best practice guidelines. Work-as-Imagined (WAI), often developed by experts and transformed into best practice guidelines, is defined as the formal work, that what managers and regulators believe should happen (4). WAI will have to to be redesigned and tailored to specific local circumstances and resources by a multidisciplinary team of physicians and key-nurses, before a CP can be built. We consider the identification of potential facilitators and barriers in the particular setting of an ICU, an important first step towards the development of our CPs (5). Clinical leadership and the conviction that peri-operative CPs play a role in the improvement of quality and safety in specific patient groups, together with a reduction of

the burden of registration, were identified as facilitators during our first steps in development and implementation of clinical pathways. An overall negative attitude existed against further protocolizing and regulation of both medical and nursing work. The existing protocols and associated registrations were experienced by nurses and physicians as time consuming processes that did not result in clear benefit for the patient. Perceived loss of autonomy following implementation of a CP was considered another important barrier that needed to be addressed and taken care of before development and implementation of a CP could start.

Implementation of a CP as a process intervention

During the design of a CP it is important to realize that this is a process intervention with the intention to strengthen the system. Although physicians and nurses want to do the right things at the right time, the circumstances and resources may not always be optimal. Caregivers need feedback mechanisms about the effects of their actions and whether or not preset goals are achieved. We presume that P-A-R cycles, together with a proper use of the variance report, can give this feedback to frontline caregivers and patients. In this way peri-operative expectations, complications and clinical outcomes in relation to adherence to the CP, can lead to a dynamic sustainable intervention. Associations with pursuit for only productive and financial indicators could make care-providers (as being frontline individuals) sceptical about new process interventions like CPs. Choosing efficiency above safety in a process may weaken it and can lead to a vulnerable system and human error can be the result (6, 7). This will have an influence on adherence and adequate use of a CP and possibly on outcome indicators.

Clinical pathway-guided care in the post-operative period has been successfully implemented for several groups of patients in many hospitals and for different medical conditions(8). In studies relating to implementation of clinical pathways in high-risk surgery patients, not all hospital wards involved in the clinical process (like PACU/ICU) were included (9-12). The main reason for this can be the assumption that in these departments the swiftness and complexity of the occurrence of derangements may not allow diagnosis and treatment according to a CP. Also, different treatment regimes and different surgical interventions make reliable comparison and evaluation of CPs difficult. The currently available studies relating to CPs do not cover the complete hospital stay, as they exclude important parts of the post-operative period. Studies of ICU care, related to CPs, focus on aspects of ICU care such as mechanical ventilation or implementation of care bundles such as the treatment of sepsis and septic shock(13, 14). The clinical outcome measures in low- and average–risk surgery mainly focus on reduction of morbidity and in-hospital length-of-stay (LOS). The relationship between protocol adherence and outcome of a CP is seldom part of the study (15-17). In our High-risk patient group we were able to

demonstrate a reduction in morbidity, readmissions and LOS. We assume that the high protocol adherences demonstrated in our studies were related to the use of a variance report which enables nurses to execute predefined actions in accordance, and within, the preset boundaries of a variance protocol without the need to consult the responsible physician first.

The first CP in the ICU in our hospital was developed for a specific group of high-volume, high-risk surgery patients. We were able to redesign and tailor the process of peri-operative care in the ICU into a CP. The development of the CP together with a "Radboud Variance report" for all cardiac surgery patients in the ICU, irrespective of the type of cardiac surgery, was initiated by our ICU-nurses because they wanted to have more clinical responsibilities. Special attention was paid to the facilitators and barriers during the implementation, training, and bedside teaching. We ascertained that the CP gave more guidance and led to better protocol adherence by using a variance report that empowered nurses to start treatment within legal boundaries. It became more explicit what they could do themselves, and exactly when they should consult the resident or staff-member. The overall protocol adherence improved significantly from 44% to 90% (p=0.01) after the implementation of the CP. We considered the adherence to the CP as Work-as-Done (WAD), in other words: informal work, how caregivers get the job done in relation to resources and workflow. Because of the high adherence, the CP almost resembles the work that has be defined by experts and transformed by them into guidelines: WAI (18). After implementation of the post-operative CP for cardiac surgery we studied trends and changes over time. We demonstrated that during our 9 years of use of a post-operative cardiac surgery clinical pathway, an increasing proportion of high-risk patients were able to follow the CP successfully, and that 95% of the patients are able to follow the CP. While more complex patients were treated according to the CP, clinical outcome improved. Development and implementation of a pre-operative optimization protocol in open transhiatal esophageal resections, a procedure representing low-volume, high-risk surgery in the ICU, was our next step. The ICU team had a wish to improve outcome in this patient group by initially analyzing their own process and adding preoperative optimization as intervention. Clinical outcomes improved, as shown by the reduction of in-hospital LOS and readmission rate to the ICU. We also identified the effects of other interventions in other patient groups in our hospital, such as the Enhanced Recovery After Surgery (ERAS) program in colorectal surgery, used by anesthesiologists and general staff in the surgical ward. Aspects of the ERAS protocol were used in many, but not all patients, in our optimization study. Unintended crossover contamination likely took place, and we conclude that CPs cannot be considered, nor studied, as isolated interventions in a closed-format ICU. We expected that the implementation of a CP for high volume, high-risk surgical procedures in the ICU could act as a blue print for low volume, high-risk surgical

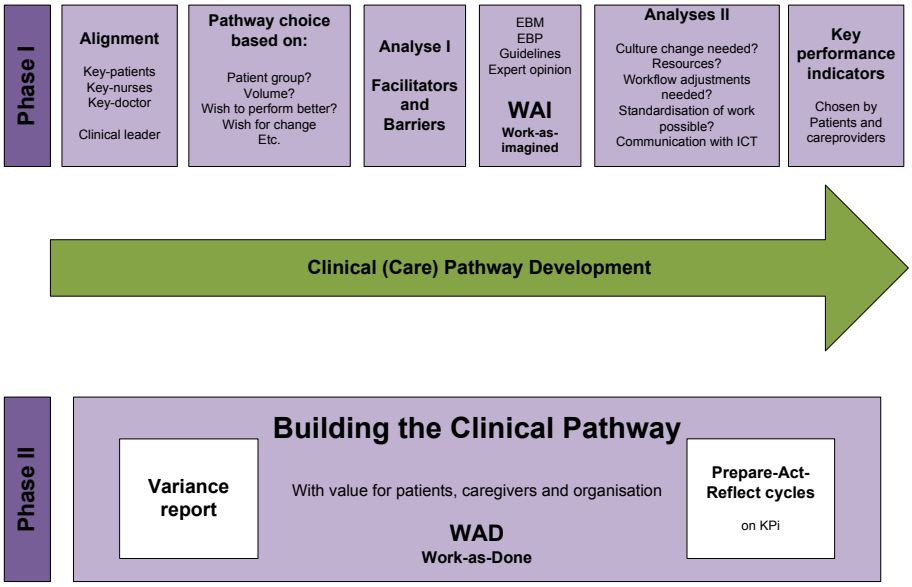
procedures in the ICU, Post Anesthesia Care Unit (PACU), and general ward. Therefore, we developed and implemented CPs for typical low-volume, high-risk procedures: open transhiatal esophagectomy procedures and pancreas surgery. In these patient groups we observed a high protocol adherence, improved clinical outcome and shorter hospital length of stay associated with the implementation of the CP. Implementation is an iterative process that takes time to become comfortable in use for all involved units. Key-nurses together with medical leadership were essential for awareness, feedback and motivation during development, implementation and the use of all CPs.

Clinical Leadership and protocols were already present and used before we developed the CPs, so several questions may emerge: What made the difference in protocol adherence and outcome following CP implementation? Are CPs applicable in other departments and hospitals as well? Frontline caregivers expressed that they wanted to work more uniformly and extend their clinical responsibilities. As a multidisciplinary group they invested time and energy in the development of a CP and built a variance report, tailored to their workflow. Educational sessions and meetings about the content and use of a CP were essential aspects of the development and implementation strategy. Key-nurses present at the ward for questions and help were crucial during implementation and continuation after implementation. The 'Radboud variance report' (see appendix), together with the development strategy was the blue print for the low-volume, high-risk surgery related CPs in the intensive care unit of our hospital. In our view, this strategy greatly facilitates development and implementation of CPs. In our expectations, this should be feasible in many departments and hospitals (Figure 1) .

Sustainability of CPs

Implementation of a CP may improve the use of multidisciplinary protocols for post-operative care for high-risk surgical patients in the ICU, however, up to now, sustainability of a CP is unknown. The research on sustainability of CPs is clearly hampered by other processes and structure interventions that may occur over time. Many structure interventions like data management, staffing levels and governance-induced regulatory rules will influence work processes and outcomes relating to these structure interventions. This has to be taken into account during follow-up, innovation and research of sustainable pathways. Clearly, other (unknown) factors may have contributed to these results as well.

Figure 1: Development flowchart of clinical pathways.



Limitations

The two most important limitations of all the studies described in this thesis are the fact that they are single center studies and the pre-post intervention study design. The intensity and duration to develop the CP, as well as the implementation process, limit the feasibility of using other study designs. Per patient randomisation and adequate blinding is clearly not feasible. A multi-center study applying a stepped-wedge approach would be needed to reach the highest quality of design. Another important limitation of our study is the fact that implementation of a CP is a culture change process for both the team and the organization. During a change process, crossover contamination will already influence the results in the control group, especially if the control group is treated during the development period of the pathway. It is a human reaction: if you feel that something is better then you will not wait to apply it. Ethical issues are also relevant. A CP based on EBM, EBP and best practice guidelines will resemble Work-as-Imagined developed by experts. As a consequence, the control group will not receive care and treatment based on these standards. We therefore used a historical control group for all described studies, because per patient randomization is considered not a feasible, nor ethical study design. Unfortunately, most studies on CP implementation share this limitation (19-23). The discussed design issues should make us aware of the possible overestimation of the observed clinical outcome differences. The wish to work uniformly in relation to culture change as aspects of a CP, makes multicenter studies of implementation and outcome of CPs a complicated procedure. Stepped wedged design may overcome this dilemma. Unfortunately, a very important ingredient will be the multidisciplinary involvement in the development of a CP, tailored to Work-as-Done. Clinical leadership, together with communication by key-physicians and key-nurses from the participating hospital to frontline caregivers could be the most important step in a successful stepped-wedged implementation of CPs. Complex process interventions like CPs were originally designed to balance quality of care and costs by focusing on better use of resources. We did not focus on costs or use of resources. We did focus on the flow of the patients' journey in relation to CP adherence and outcome, not associated with currencies and governance related control systems.

Future Perspectives

Despite the above mentioned limitations, empirical evidence and conclusions are firm: the use of a CP in high-risk surgery is feasible and safe. Moreover, it is likely related to a better clinical outcome. The analysis of facilitators and barriers in the development process could be the reason for a better protocol adherence and could be associated with better caregiver satisfaction. These effects of empowerment of nurses and physicians together with quality in work balance (viewed as being valued) could be studied within CPs. Measurement of team climate, annual interviewsand trends in absenteeism could be analyzed within departments. The P-A-R cycle can also be an instrument to identify human errors, which are often actually process or system errors and reduction of these errors should be part of a dynamic remodelling of a CP.

Patient-Centred-Care-Pathways

The described pathways in this thesis were originally developed to integrate nursing and medical protocols in to multidisciplinary care plans for high-risk surgery patients, with the intention of working uniformly, safely and with the intention of resulting in better clinical outcomes. Another intention was the empowerment of ICU nurses, based on education, communication and trust in each other as a professional. Future CPs should be built around, but also with, patients. Shared-decision-making and person-centered-care needs to be the key components of a CP. Patient representatives (or key-patients) may claim their part in the development of CPs together with key-physicians and key-nurses and P-A-R-cycle results have to be shared with them. This may seem a contradiction to the described CPs, where standardized, safe and efficient care were the main goals. In the ICU, where swift hemodynamic and respiratory changes are often observed followed by adequate actions, patients and their relatives will probably have a different role in the development of a CP. But, for the future we should focus on the definition of a Care Pathway by the European Pathway Association (EPA): "A clinical pathway explicitly states the goals and key elements of care based on Evidence Based Medicine (EBM) guidelines, best practice and patient expectations by facilitating the communication, coordinating roles and sequencing the activities of the multidisciplinary care team, patients and their relatives.

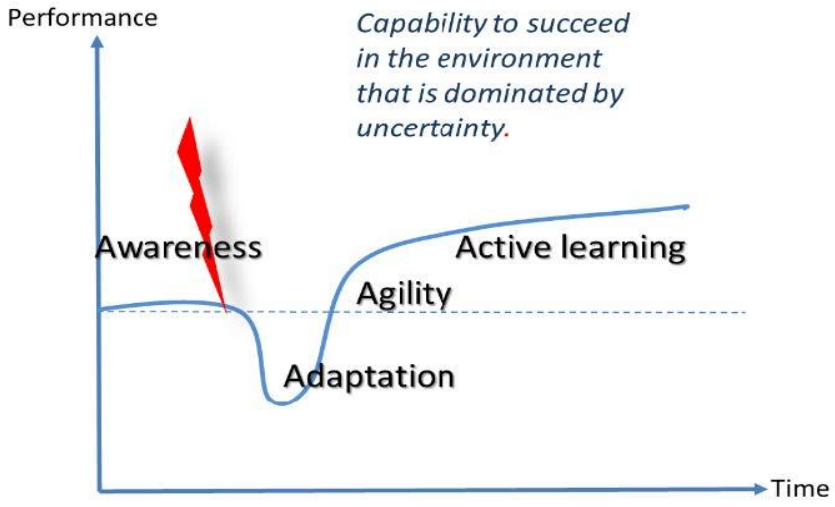
We should be aware that some patients are not fit for all the aspects of a CP. The preset goals for patients with more co-morbidities can be different. In our sustainable cardiac surgery CP we were able to identify a patient group which was never included in the CP. These patients were expected to be unable to follow our clinical pathway and some received a personalized pathway. Communication and information to the patients and their families about this expected more difficult journey in this group of patients will open the pathway to shared-decision-making. Person-centred limitations in care, and sometimes the

mutual decision not to start treatment, can be the result of this shared decision. This has to be part of the shared-decision making process and should be clear for patients and their treatment team of physicians and nurses, before starting the person-centered CP. Work-as-Done should resemble as much as possible Work-as-Imagined and should be integrated in a safe patients' journey for all patients not only for those fit for a specific CP. Patient reported outcome measures will probably be the tool for research in this field.

Care Pathways as a tool to enhance Resilience in our care system

Medical misadventures within our medical system do have tremendous effects on the resilience of a team and processes. Traditional risk management will focus on the weakest link in the system, resilience analysis will draw its attention towards a "soft landing " to reduce collateral damage and adapt and recover after an incident (24). The time to recover from such an event is different between caregivers, departments, and hospitals. We assume that a CP can have an effect on the resilience profile, developed by Imola et al. A CP may reduce adaptation time from an adverse event, by the adequate use of the P-A-R-cycle and knowledge of the work process as Work-as-Done (25).

Figure 2: Resilience profile. L.Ilmola IIASA IRGC (2016). Resource Guide on Resilience. Lausanne: EPFL International Risk Governance Center. *v29-07-2016.*



This emphasizes the importance in understanding why things usually go right and in the right flow, and our obligation to develop the circumstances that as many things as possible can go right (Safety-II). Instead of the primary focus on analyzing causes and contributory factors of adverse outcome where the safety management response will be the elimination of the cause and building improved or more barriers (Safety-I) as currently applied (26). Safety-II should become the driver of the development and use of CPs in the patients' journey. Because a dynamic variance report in a CP will drive on preset goals and early actions to stay on the safe side of the pathway, instead of building more barriers (especially more registration , checkboxes and banners) to prevent more harm.

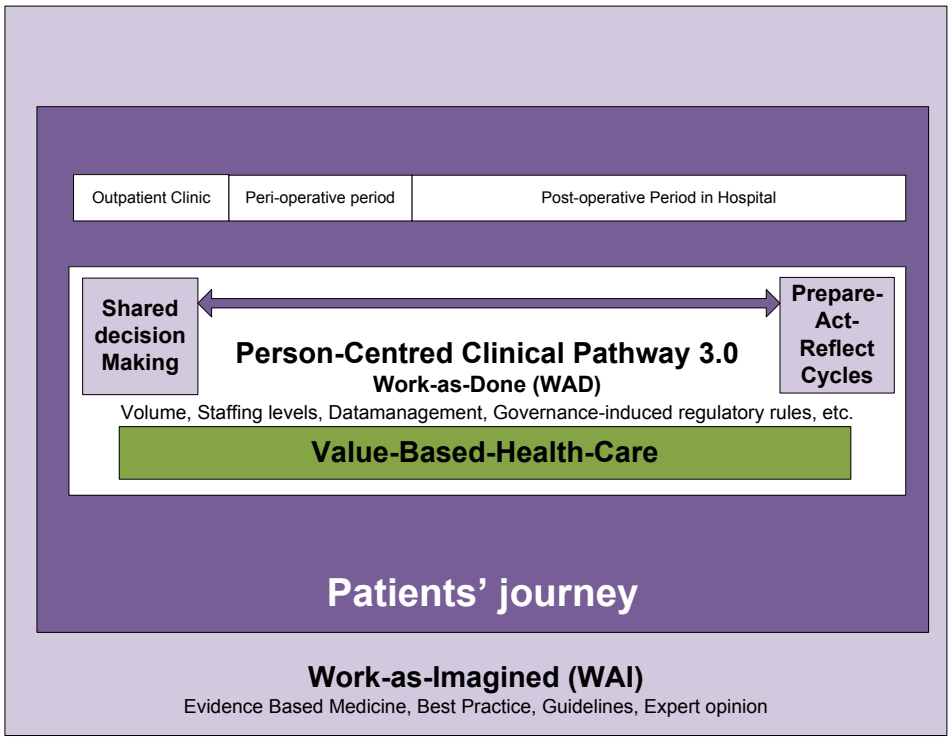
The role of CPs in quality and safety in relation to our health care reimbursement system

The financial system relating to reimbursement and costs in health care is not directly associated with a small amount of key performance indicators for protocol adherence, adequate use of care pathways or outcome. Nowadays, the existence of written protocols and guidelines in the different care processes seem to be, together with registration of many indicators, the condition needed for reimbursement and accreditation. Many indicators have to be provided repeatedly to different control systems that are not intertwined or connected with each other. Moreover, many indicators are not recognized as key-performance indicators by frontline care professionals. The ever increasing registration burden and subsequent outgrowth of systems, jobs and commissions to analyse the registered items (based on Work-as-Imagined (WAI)) are seldom related to the difficult choices that are made by frontline caregivers (resulting in Work-as-Done (WAD). An important step forward could be the implementation of CPs, with only a small amount of selected key performance indicators built into the system by frontline caregivers (and patients) and, actually related to quality and safety. Deviations or variances from preset goals for care and clinical outcome (as part of the CP) could be the only registered items by frontline caregivers. The essence will be that the use of the CP, with a P-A-R cycle, is a team effort based on doing the right things at the right time with an incentive for continuous improvement. Governance registration rules and outcome presentations should be related to protocol adherence and the well chosen key-performance indicators related to the CP. As a result, reimbursement or financial incentives should be on patients' health in times of illness with the least complications and setbacks. If dynamic CPs are built into our hospital electronic systems (both intra-disciplinary and multidisciplinary), and connected with each other, this will lead to better team work, communication and circumstances, further facilitating protocol adherence. As a consequence, provided care is expected to be more efficient and safe. The short cycle P-A-R cycles relating to the key performance indicators chosen by frontline care-givers, will result in useful feedback and agile interventions to put the patient, together with the process, back on the pathway track. Control systems that seem to be in control nowadays can be reduced and better systems can be used through reinforcement of frontline care-givers instead.

New process interventions in provided care, like CPs, should not increase workload and stress on our health care system and health care providers, and have to be based on flow and should be patient-centered. This flow, observed in the patients' journey, should resemble agile short-cycle new power. This will hopefully replace the old power associated currency and control systems held by few (27). Research on the use of CPs in relation to provided care during illness, could be the beginning of a new reimbursement system in health care.

The result of a successful CP implementation will be the establishment of new principles and the cycle can start again. In this continuous dynamic cycle of CP development and renewal, patients, together with caregivers, have to be the builders of these pathways. Contact with information technology personnel in their hospitals has to be on a short cycle basis, to make it possible for these ICT colleagues to build the variance report together with the chosen Key-performance-indicators (KPis) of the pathways into the Patient Data Management System (PDMS) aligned to the clinical workflow. This provides patients and caregivers with steering information on Kpis and clinical outcome. This essential information for patients and caregivers (being an aspect of the P-A-R-cycle) has to be more real-time. This shared knowledge will be the base for building shared decision making, patient-centered-care together with aspects of value-based- health-care into the clinical pathways 3.0.

Figure 3: Flowchart: Clinical Pathway 3.0



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Nederlandse Samenvatting

Ontwikkeling, implementatie en evaluatie van intensive care gerelateerde klinische paden voor chirurgische ingrepen met een hoog risico: effecten van een proces interventie.

Klinische paden of zorgpaden zijn ontwikkeld om optimale zorg te geven aan een specifieke patiënten groep met als doel verschillen in aangeboden zorg tussen individuele patiënten en individuele zorgverleners weg te nemen. Oorspronkelijk zijn klinische paden ontwikkeld om de verschillen tussen kwaliteit van zorg en de kosten van zorg in balans te brengen. Daarbij ligt doorgaans de focus op een beter gebruik van voorzieningen, maximale kwaliteit van zorg en het minimaliseren van de tijd tussen diagnose en behandeling. Zowel de ontwikkeling, als de implementatie van klinische paden worden gezien als complexe procesinterventies en worden meestal ingezet in voorspelbare, niet complexe procedures in de zorg. Wij ontwikkelden en implementeerden verschillende klinische zorgpaden waarbij verpleegkundige en medische protocollen geïntegreerd werden in een multidisciplinair zorg plan voor patiënten die een chirurgische procedure moeten ondergaan met een hoog peri-operatief risico op complicaties. De inhoud van een zorgpad bestaat niet uitsluitend uit multidisciplinaire- of intradisicplinaire protocollen, maar is eveneens een dag- tot- dag zorgplan dat alle behandelingen en acties beschrijft, die nodig zijn binnen een vooraf bepaalde periode, om optimale zorg te kunnen leveren aan de patiënt. In onze ICU werd daarom naast het zorgpad een zogenaamd "variantie rapport" ontwikkeld, dat het verpleegkundigen mogelijk maakt om, binnen de grenzen van de BIG-wet (Wet individuele beroepen Gezondheidszorg), handelingen te starten. Alle patiënten in de beschreven onderzoeken ondergingen een vorm van hoog-risico chirurgie en werden in de peri-operatieve fase opgenomen op de intensive care unit (ICU) van ons ziekenhuis voor bewaking en ondersteuning van hun vitale functies. Onze hypothese was dat een procesinterventie als de ontwikkeling en implementatie van een klinisch pad op de ICU voor hoog-risico chirurgie, samen met het daadwerkelijk gebruik daarvan, de kwaliteit van zorg zal verbeteren. Dit kan leiden tot een vermindering van het aantal ernstige complicaties en verkorting van de opname duur. Een klinisch pad is gebaseerd op evidence based medicine (EBM), best practice afspraken (BP) en richtlijnen, doorgaans opgesteld door experts. Dit betekent in de ICU, dat een klinisch pad kan bestaan uit een uniform mutidisciplinair protocol samen met een vastgelegd uur-tot-uur schema voor een specifieke patiënten groep. In dit klinisch pad staat beschreven welke interventies en acties nodig zijn, indien veranderingen en afwijkingen van het pad gesignaleerd worden . Dit schema zal moeten focussen op herkenning van vitale bedreigingen en afwijkingen (deviaties) van het klinisch pad door verpleegkundigen en zal hen in staat moeten stellen vroegtijdig een behandeling te kunnen starten. Dit alles binnen de grenzen van de voorgeschreven vari-

anties waarop gehandeld mag worden. De ontwikkeling, implementatie en evaluatie van een klinisch pad in de ICU zal onderdeel moeten zijn van een Prepare-Act-Reflect cyclus (P-A-R cyclus). Dit moet een dynamisch proces dat verdere verbeteringen in de te geven zorg faciliteert. Structuurinterventies in een systeem, zoals verandering in aantal zorgverleners, aantal specifieke operatieprocedures of Patiënt Data Management Systeem, samen met veranderingen in onderliggende evidence en richtlijnen, zullen effect hebben op de uitvoering van protocollen door mensen op de werkvloer. Richtlijnen worden doorgaans ontwikkeld door experts en hebben tot doel uniformiteit van werken echter daarbij wordt doorgaans niet naar de lokale situatie en/of de bestaande lokale systemen gekeken. De ideale situatie ontstaat als aan alle randvoorwaarden wordt voldaan en het werk kan worden uitgevoerd conform de bestaande standaarden of best practices welke gebaseerd zijn op wetenschappelijke onderzoek en consensus, het zogenaamde Work-as-Imagined (WAI). Hiertegen over staat de invulling van WAI op de werkvloer. Het uitvoeren van het werk naar beste kunnen met de bestaande mogelijkheden en voorzieningen, het zogenaamde Work-as-Done (WAD). Indien we deze gedachte vertalen naar een goed klinisch pad dan zullen alle acties moeten bijdragen aan en resulteren in snelle aanpassingen, indien afwijkingen geconstateerd worden. Hiermee komt WAD zo dicht mogelijk bij WAI.

In het eerste deel van dit proefschrift ligt de focus op het bepalen van de mogelijkheid en haalbaarheid om een klinisch pad te ontwikkelen en te implementeren met een post-operatief uur-tot-uur plan voor hartchirurgische patiënten in de ICU. Vervolgens leggen we de focus op trends in de tijd, na implementatie in hoog-volume hoog-risico chirurgie zoals hartchirurgie. Analyse van in positieve zin bijdragende, (faciliterende) omstandigheden en bestaande barrières binnen deze structuur of op proces niveau zijn onderdeel van dit proefschrift.

Het tweede deel van dit proefschrift beschrijft de ontwikkeling en implementatie van klinische paden in laag-volume, hoog-risico chirurgie in de ICU, zoals pancreas chirurgie en slokdarmchirurgie, waarbij het klinisch pad van de hartchirurgie als blauwdruk is gebruikt. We beschrijven de ontwikkeling van een pre-operatief optimalisatieprotocol, voor patienten die een open slokdarm resectie ondergaan met buismaag reconstructie in een closed-format ICU. Daarnaast beschrijven we de ontwikkeling en implementatie van een klinisch pad voor operaties aan de pancreaskop (Whipple procedure), van verwijzing naar de polikliniek Heelkunde tot aan ontslag uit het ziekenhuis. In beide studies bestuderen we tevens effecten gerelateerd aan de verschillende uitkomstmaten in deze patiënten groepen.

In **hoofdstuk 2** wordt de ontwikkeling en implementatie van een klinisch pad met een variantierapport, beschreven samen met de evaluatie van een post-operatief klinisch pad voor alle hartchirurgische patiënten in de ICU. De ontwikkeling van dit klinisch pad hangt sterk samen met de wens van de intensive care verpleegkundigen in ons ziekenhuis, om meer autonomie te krijgen in het behandelproces van de patiënt. Het variantierapport maakt het mogelijk voor verpleegkundigen om, vooraf beschreven acties uit te voeren in overeenstemming met vooraf afgesproken vastgestelde grenzen. Een voorbeeld is het starten van vaso-actieve medicatie bij lage bloeddruk of middelen die de stolling bevorderen, indien na hartchirurgie het bloedverlies uit de drains te hoog is. Deze acties worden gestart zonder tussenkomst van een arts, uiteraard bij twijfel of onvoldoende effect wordt de (volgende) te ondernemen stap overlegd met een arts. Bij afwijken van het te verwachten postoperatieve pad, in deze hoog-volume hoog-risico chirurgische patiëntengroep, beschrijft het klinisch pad alle multidisciplinaire activiteiten in het postoperatieve ICU proces, die dan ondernomen kunnen worden om de patiënt weer op het juiste pad te brengen. Een klinisch pad in de ICU van het Radboudumc heeft tot doel dat, bij vroegtijdige herkenning van een mogelijk afwijkend beloop (deviaties), door verpleegkundigen behandeling gestart kan worden, die voorheen beschouwd werd als een aan artsen voorbehouden interventie. Deze behandelingen, zonder tussenkomst van een arts, vallen binnen de grenzen van de Nederlandse BIG-wet (Wet Individuele Beroepen Gezondheidszorg). Het doel van deze studie was ten eerste de haalbaarheid van het ontwikkelen en implementeren van een klinisch pad voor alle hartchirurgische patiënten in de ICU. De ontwikkeling van het klinisch pad gebeurde gelijktijdig met de ontwikkeling van een uniek variantierapport ('Radboud variance model') door de ontwikkelaars, artsen en verpleegkundigen. In dit model worden alle multidisciplinaire activiteiten in de ICU beschreven. Het ontwikkelproces, samen met de scholing en implementatie, duurde ruim 18 maanden. De verwachting was dat door het klinisch pad en het geven van behandelingsbevoegdheden aan verpleegkundigen, adherentie aan onderliggende protocol hoger zou zijn. Het doel was dat protocol adherentie boven 80% zou komen. Daarnaast analyseerden wij de resultaten van deze protocoladherentie in relatie tot de uitkomsten in de interventiegroep, die volgens het klinisch pad werd behandeld. Deze groep werd vergeleken met een "propensity matched" historische controle groep. De controle groep werd een jaar voor de implementatie van het klinisch pad behandeld, conform de bestaande separate niet-geïntegreerde verpleegkundige en medische protocollen en zonder "variantierapport" waarop zij mochten handelen. In een periode van 4 maanden werden 84 opeenvolgende patiënten geïncludeerd in het klinisch pad en deze werden vergeleken met 162 gematchte controle patiënten, die in het jaar voor de implementatie werden behandeld. We constateerden dat bij klinisch pad patiënten vaker en eerder (binnen 30 minuten) adequate behandeling werd gestart door verpleegkundigen, bij aanwezigheid van afwijkende electrolyt waarden (96% vs 47%, $p<0.001$), eerder adequate acties op bloeddruk veranderingen werden gestart (90% vs

49%, p<0.001) en een snellere behandeling werd ingezet, indien sprake was van een toegenomen bloedverlies uit de thoraxdrains (90% vs 10%, p<0.001). Deze studie was niet gepowered om verschillen in opnameduur in het ziekenhuis of de ICU, heropname ICU of mortaliteit aan te tonen. Deze studie ging om haalbaarheid van het ontwikkelen van en implementatie van het klinisch pad.

We concludeerden dat het haalbaar is een, voornamelijk door verpleegkundigen uitgevoerd, uur-tot-uur klinisch pad te implementeren in de ICU voor postchirurgische hartchirurgische patiënten. Tevens toonden we aan dat het gebruik van een KP voor alle hartchirurgische patiënten resulteerde in een snellere start van de behandeling en beter georganiseerde postoperatieve behandeling in de ICU voor deze patiëntengroep. Dit betekende een betere bloeddrukregulatie, betere electrolytregulatie, temperatuurregulatie van de patiënt, snellere weaning van de beademing en extubatie evenals snellere adequate acties op verhoogd bloedverlies uit thoraxdrains. Deze implementatiestrategie, samen met het gebruik van een "variantierapport" ontwikkeld in een hoog-volume hoog-risico patiëntengroep, werd gebruikt als blauwdruk voor de ontwikkeling en implementatie van een klinisch pad voor laag-volume en hoog-risico chirurgische procedures gerelateerd aan de ICU.

Na de implementatie van het klinisch pad voor de postoperatieve hartchirurgische patienten in de ICU, wilden we trends en veranderingen over een tijdsperiode bestuderen in de totale groep van meer dan 7500 hartchirurgische patiënten, die behandeld werden in ons ziekenhuis in de negen jaren die volgden op de implementatie van het klinisch pad. Deze retrospectieve cohort studie wordt beschreven in **hoofdstuk 3**. Het primaire doel van de studie was trends te bestuderen in inclusie en exclusie van patiënten in het klinisch pad. De patiëntenkarakteristieken werden geanalyseerd per periode van drie jaar. Het secundaire doel van de studie was om trends te bepalen gedurende de tijd en tussen de groepen, met betrekking tot opnameduur op de ICU en opnameduur in het ziekenhuis, re-operaties, heropnames ICU, de ziekenhuismortaliteit en de 1-jaars mortaliteit. De effecten gedurende deze tijdsperiode en de klinische uitkomsten werden onderzocht in drie patiëntengroepen, patiënten die geïncludeerd werden in het klinisch pad, patiënten die secundair geëxcludeerd werden binnen 48 uur na de operatie , of patiënten die nooit geïncludeerd werden in het klinisch pad. Tevens werd een subgroep analyse verricht in de groep patiënten met een hoge Log EuroSCORE >10. Deze retrospectieve cohort studie werd verricht in de totale groep van 7553 patiënten, die geopereerd werden tussen 1 januari 2007 en 31 december 2015. We identificeerden drie patiëntengroepen: patiënten die behandeld werden volgens het klinisch pad (n=6567), patiënten die geëxcludeerd werden uit het klinisch pad binnen de eerste 48 uur na chirurgie (n=633) en een groep van patiënten die nooit geïncludeerd werden in het klinisch pad (n=353). De implementatie

van een nieuw Patiënt Data Management Systeem (PDMS) in 2013 beschouwden wij als een complexe structuurinterventie, daarom hebben we besloten ook te kijken naar de effecten van de implementatie van het nieuwe PDMS binnen onze registratie. We hadden de verwachting dat de implementatie van het PDMS gevolgen zou kunnen hebben voor allerlei processen die een rol spelen bij patiënten informatie inclusief patiëntenzorg en veiligheid. Na de implementatie van het klinisch pad steeg het percentage patiënten, dat behandeld werd conform het klinisch pad, van 74% in het jaar na de implementatie van het pad, naar 95% in 2012 en bleef stabiel gedurende de laatste 3 jaren van dit onderzoek. De mediane [IQR]Log EuroSCORE van patiënten die behandeld werden volgens het klinisch pad steeg van 2.91 [1.54-5.71] naar 3.30 [1.75-6.25] (p=0.016). Dit toont aan dat zorgverleners minder bedenkingen hadden om meer complexe patiënten volgens het klinisch pad te behandelen. Ondanks het feit dat patiënten met meer comorbiditeit volgens het klinisch pad werden behandeld, daalde de ziekenhuis opnameduur van mediaan 6 dagen [IQR:4-8] naar mediaan 5 dagen [IQR:3-7] in de klinisch pad groep ($p<0.001$). Over het algemeen daalden in de klinisch pad groep de ziekenhuismortaliteit en de 1–jaars mortaliteit respectievelijk van 1.5 naar 1.1% en van 3.7 naar 2.9%, (beiden $p<0.05$). Patiënten met een Log EuroSCORE>10 werden doorgaans vaker geëxcludeerd van het klinisch pad ($p<0.001$). Patiënten met een Log EuroSCORE>10, die in het klinisch pad behandeld werden, hadden een kortere ICU opname duur en ziekenhuis opnameduur vergeleken met de geëxcludeerde patiënten met een Log EuroSCORE>10, ($p<0.001$). We observeerden dat, registratie en correcte labeling van patiënten in het PDMS, naar hun postoperatieve zorgpad (inclusie of exclusie) moeizaam was (ondanks een papieren schaduwsysteem). De implementatie van het nieuwe PDMS had geen invloed op de uitkomstdata binnen de subgroepen. In de subgroepanalyse observeerden we dat ook de hoog risico patiënten met een Log EuroSCORE > 10 in staat bleken het klinisch pad succesvol te volgen. Uiteindelijk verwachten we dat dit continue leerproces van klinisch pad-geleide zorg ons zal leiden naar meer gepersonaliseerde zorgpaden voor patiënten met een hoge Log EuroSCORE en naar gezamenlijke beslissingen tussen patiënt en arts en meer gepersonaliseerde zorg in de toekomst. Deze studie illustreert de duurzaamheid van een klinisch pad na implementatie voor hartchirurgische patiënten. Klinische uitkomsten verbeterden terwijl meer complexe patiënten behandeld konden worden volgens het klinisch pad. We realiseren ons dat andere factoren binnen zorgprocessen ook kunnen hebben bijgedragen in de verbetering van de uitkomsten gedurende deze jaren.

In **hoofdstuk 4** wordt een observationele evaluatie studie beschreven, gericht op pre-operatieve optimalisatie van de centraal venueze zuurstof saturatie ($ScvO_2$), in een groep patiënten een transhiatale oesophaguscardia resectie met buismaagreconstructie ondergingen, in verband met de aanwezigheid van slokdarmkanker, cardia-carcinoom of hooggradige dysplasie. De gedachte was dat verbetering van de zorg binnen de intensive

care afdeling, invloed kan hebben op de uitkomsten voor deze patiëntengroep, ook al is dit slechts een onderdeel van het totale proces. De verwachting dat de patiënt in betere hemodynamische conditie de operatie in gaat, kan dat een positief effect hebben. De patiënten werden daarom pre-operatief opgenomen op de ICU voor hemodynamische optimalisatie. We onderzochten de relatie tussen pre-operatieve optimalisatie met een specifieke set van postoperatieve complicaties, in een geselecteerde groep van 68 opeenvolgende patiënten. Deze interventie groep werd vergeleken met een historische controle groep van 32 patiënten, die geopereerd werden zonder dat ze pre-operatief geoptimaliseerd werden in de 2 jaar voorafgaande aan deze optimalisatie studie. Onze hypothese eruit dat pre-operatieve optimalisatie in een geselecteerde groep van laag-volume hoog-risico chirurgische patiënten, zou resulteren in minder postoperatieve complicaties. Optimalisatie startte één dag vooraf aan de slokdarm resectie met buismaagreconstructie in de ICU. We gebruikte een matrix die verpleegkundigen en arts-assistenten in staat stelde om de optimalisatie te starten door het toedienen van vloeistof infusie en/of inotropica, indien de gemeten $ScvO_2$ minder was dan 70%. In de geoptimaliseerde groep was de mediane [IQR] vloeistof infusie 1415 ml[904-1993] en 8.8% van de geoptimaliseerde patiënten kreeg inotropica om de $ScvO_2$ te verhogen. Een $ScvO_2$ >70% werd bij 77 % van de geoptimaliseerde patiënten bereikt en de delta $ScvO_2$ nam toe mediaan [IQR] 4 [0-7]%. Patiënten die geen $ScvO_2$ >70% behaalden, hadden vaker cardiovasculaire comorbiditeit (73% vs 37%,p=0.02). Postoperatief trad sepsis op bij 4% van de geoptimaliseerde patiënten en bij 16% van de controle patiënten (p=0.004), naadlekkage werd gediagnostiseerd bij 12% van de geoptimaliseerde patiënten versus 25% van de controle patiënten (p=0.14). Verder leek er sprake van een trend dat geoptimaliseerde patiënten minder vaak werden heropgenomen op de ICU (p=0.07) en hadden deze patiënten een korter verblijf in het ziekenhuis, namelijk mediaan 10 [IQR 9-15] vs mediaan 16 [IQR 13-35] dagen (p<0.001) in de controle groep. De postoperatieve beademingduur van de geoptimaliseerde groep was mediaan 5.2 [IQR 3.7-7.5] vs 8.0 [IQR 3.5-23.7] uren in de controle groep (p=0.03). Er was geen postoperatieve 30-dagen mortaliteit in de geoptimaliseerde groep, terwijl drie patiënten overleden in de controle groep. We concludeerden dat pre-operatieve hemodynamische optimalisatie geassocieerd was met een kortere opname duur in het ziekenhuis, minder infectieuze complicaties, kortere beademingsduur en een lagere mortaliteit. Het bloed verlies en het gebruik van bloed producten was niet toegenomen in de groep patiënten, die preoperatief hemodynamisch geoptimaliseerd werden op geleide van hun $ScvO_2$ in de ICU. Deze resultaten suggereren dat preoperatieve optimalisatie voor deze specifieke patiënten groep van hoog-risico chirurgische patiënten van voordeel zijn en een reductie geeft van verschillende specifieke uitkomstparameters. We moeten hierbij wel opmerken dat dit een single-center, pre-post interventiestudie betreft en dat interventies die gedurende die periode werden ingevoerd op andere afdelingen, zonder dat wij daarvan op de hoogte waren, eveneens effect kunnen hebben gehad.

In hoofdstuk 5 beschrijven we het proces van ontwikkeling en implementatie van een klinisch pad in de ICU en in de Post-Anaesthesia-Care-Unit (PACU) voor patiënten die een pancreaticoduodenectomie ondergingen. Het klinisch pad pancreaschirurgie had vanaf het begin tot doel een continue flow door het ziekenhuis te creëren, van verwijzing naar de polikliniek tot aan ontslag uit het ziekenhuis na de operatie. De essentiële elementen van dit klinisch pad waren: intra-operatieve en peri-operatieve vloeistofrestrictie, conform het Enhanced Recovery After Surgery (ERAS) programma, strikte pijn regulatie, vroege mobilisatie, vroege drain en maaghevel verwijdering en het vroeg starten van orale intake (zoals in ERAS, Kehlet & Dahl, Lancet 2003). Postoperatief stond eveneens vroege herkenning van de Vitaal Bedreigde Patiënt centraal. Early warning scores (EWS) werden minstens één maal per 8 uur gemeten en indien nodig vaker, op indicatie van de verpleegkundige. Dit ging samen met duidelijke instructies voor het actief starten van de behandeling in overeenstemming met het "variantierapport". De ontwikkeling en implementatie van dit klinisch pad, dat meerdere afdelingen betrof duurde meer dan 12 maanden. Een prospectieve cohort studie werd verricht in een groep van 95 opeenvolgende patiënten, die behandeld werden conform het klinisch pad in de periode september 2014 tot en met september 2016. Deze groep werd vergeleken met een historische controle groep (n=52) die behandeld was met het traditionele regime volgens de matrix die ten grondslag lag aan het klinisch pad. Het doel van het onderzoek was, het bepalen of de implementatie van het klinisch pad veilig en effectief was, in relatie met de incidentie van postoperatieve complicaties zoals beschreven volgens de Clavien-Dindo classificatie (Dindo& Clavien, Annals of Surgery 2004). Secundaire eindpunten waren, de hoogte van postoperatieve vochtbalans, het optreden van gastroparese, de protocol adherentie voor mobilisatie, drain en maaghevel verwijdering, radiologische en chirurgische re-interventies, ICU heropname, opname duur ziekenhuis, ziekenhuis heropname en mortaliteit. De procesevaluatie van de klinisch pad groep toonde aan dat protocoladherentie bij alle componenten van het klinisch pad, op de verschillende door de patiënt bezochte klinische afdelingen, boven 80% was. Ernstige complicaties volgens de Clavien-Dindo Classificatie graad ≥3, was significant lager in de klinisch pad groep (13%) in vergelijking met de controle groep (27%); p=0.02. Opname duur in het ziekenhuis was eveneens significant korter in de KP groep, mediaan 10 dagen [IQR: 8-15], vergeleken met de controle groep, mediaan 13 dagen [IQR: 10-18]; p=0.02. Het gebruik van het klinisch pad voor pancreaticoduodenectomie was geassocieerd met een significante reductie van perioperatieve morbiditeit, zoals een reductie van gastroparese (p<0.001) en minder radiologische drainages (p=0.04). Essentiële nieuwe onderdelen van dit klinisch pad waren een geplande barrière en facilitator analyse, inclusie van een "variantierapport" analyse en herhaalde P-A-R cycli in het ontwikkelen en implementeren van het protocol, uitgevoerd door een multidisciplinair team. We concludeerden dat de ontwikkeling, implementatie en het gebruik van het klinisch pad gedurende het gehele

ziekenhuisverblijf voor patiënten die een pancreaticoduodenectomie onder gaan, een meerstaps procedure is welke uitvoerbaar en veilig is gebleken.

We reflecteren op de behaalde resultaten en de mogelijke noodzaak voor duurzame klinische paden, evenals de ontwikkeling van gepersonaliseerde zorgpaden voor hoog-risico chirurgie in **hoofdstuk 6.** Alhoewel het concept van van klinische paden al meer dan twee decennia bestaat, heeft brede implementatie op de ICU tot op heden niet plaats gevonden binnen de hoog-risico chirurgie. Doorgaans worden uitsluitend bepaalde aspecten van intensive care behandeling, zoals beademing of vroege sepsis behandeling volgens een bundel, geïmplementeerd. Potentiële voordelen beperken zich niet tot kosteneffectiviteit, de mogelijkheden op het gebied van verbeteren van klinische uitkomsten zijn groot. De European Pathway Association, die paden ontwikkelde in o.a. acute zorg, COPD en heupfracturen, concludeerde, dat essentiële interventies, op basis van Evidence Based Medicine of Evidence Based Practice, beter worden uitgevoerd na implementatie van een klinisch pad vergeleken bij standaard geprotocolleerde zorg. Wij bediscussiëren dat een succesvol geïmplementeerd klinisch pad de kwaliteit van zorg kan verbeteren, en kan leiden tot een reductie van complicaties. Het is aannnemelijk dat dit tevens resulteert in verbetering van de Patient Reported Outcome Measures (PROMs) en minder verspilling van voorzieningen. Het is daarbij essentieel dat alle betrokken zorgverleners, binnen het klinisch proces, aangehaakt zijn evenals de patiënt en zijn famlie. Als het proces duidelijk is voor iedereen, dan zullen afwijkingen van het zorgpad sneller herkend worden en dit zal dan resulteren in snellere interventies om de patiënt terug te brengen in het zorgpad, in overeenstemming met de voorafgestelde geïndividualiseerde doelen. Op deze wijze kan een klinisch pad bijdragen aan de empowerment van verpleegkundigen, physician assistents en arts-assistenten en daardoor aan veilige beslissingen voor de behandeling van de patiënt die tijdig worden toegepast. Patiënten zullen zich mogelijk veiliger voelen gedurende het behandelproces en kunnen in staat gesteld worden om hun gepersonaliseerde klinisch pad te volgen.

De algemene discussie met tevens ideeën voor de toekomst worden beschreven in **hoofdstuk 8** met focus op de relatie tussen proces interventies zoals de ontwikkeling en implementatie van klinische paden en klinische uitkomsten. We bediscussiëren stappen die wij daarin belangrijk vinden.

Appendix klinisch pad hartchirurgie

Figure 1: Klinisch pad

Cardio Thoracale Chirurgie

Variantie HD stabiliteit	Actie	beleid arts, tijdstip en actie
ABP ↓ en CVD ↓ wedge ↓ en CI ↓ of ABP ↓ en CVD ↓ of normaal en CI normaal	□ indien Nicardipine: afbouwen / stoppen □ indien NTG of andere vasodilatantia : overleg arts □ bij HB < 5,0 1 PC geven □ bij HB > 5,0 mmol/l of onbekend: 250 ml NaCl 0,9% (maximaal 750 ml NaCl 0,9% of 1 PC en 500 ml NaCl 0,9%) voorzichtig vullen bij matige of slechte ventrikel Bij onvoldoende resultaat : arts waarschuwen	□ 1 PC Hb < 5,0 mmol/l …uur □ 1e NaCl 0,9% 250 ml……..uur □ 2e NaCl 0,9% 250 ml……..uur □ 3e NaCl 0,9% 250 ml……..uur

	actie	beleid arts, tijdstip en actie
ABP ↑ en CVD en wedge normaal *en* *HF > 90/min*	□ sluit ischemie , onrust, pijn en rillen uit. □ inotropie?, iom arts afbouwen □ i.o.m. arts metoprolol toedienen	□ □ □
ABP ↑ en CVD en wedge normaal *en* *HF < 90/min*	□ sluit ischemie , onrust, pijn en rillen uit.! □ inotropie?, iom arts afbouwen □ goede LVF: start nicardipine (cave SaO_2↓ door shunting) □ slechte of matige LVF : overleg met arts □ bij onvoldoende resultaat overleg met arts	□ Bij toediening Nicardipine: □ SpO_2 daling > 5% < 2 uur na start nicardipine □
Overige combinaties van HD afwijkingen (ook sinusritme > 90/min)	□ controleer uitgangssituatie, overleg met arts	□

	actie	beleid arts, tijdstip en actie
Nieuwe ritme- geleidingsstoornissen	□ maak ECG □ overleg met arts	Ritmestoornis: □
PM ritme: paced en/of sensed niet goed	□ controleer werking / protocol □ overleg met arts	□
ST segment afwijkingen	□ maak ECG □ overleg met arts □ stel ST segment alarm bij volgens protocol	□ NTG gestart □ Troponines vervolgen □ extra pijnbestrijding

Variantie Uitscheiding	actie	beleid arts, tijdstip en actie
Urineproduktie< 0,5 ml kg	□ controleer doorgankelijkheid □ overleg met arts	□
Thoraxdrainproduktie = 0 ml / uur	□ controleer doorgangkelijkheid drains □ overleg met arts indien drainproduktie 0 ml. blijft	Oorzaak :
1e 4 uur p.o. Thoraxdrainproduktie : * 1e uur ≥ 150 ml/uur, * 2e/3e uur ≥100ml/uur * daarna elk uur ≥50 ml/uur (zonder reden zoals, detuberen etc)	□ sereus drainvocht - licht arts in **geen sereus drainvocht dan** : □ controle ACT → > 150 sec. □ controleer op overgevoeligheid protamine / garnalen □ → geef 2500 E protamine iv **indien onvoldoende resultaat of normale ACT** : □ controleer ACT, PTT, APTT, Hb, Ht en trombo's □ overleg arts PC's op voorraad op BTD	□ ACT : .....sec. - tijd : .... □ 2500 E protamine: tijd : ... □ □

Figure 1: Continued

Variantie Pijn en Sedatie	actie	beleid arts, tijdstip en actie
Patiënt krijgt sedatie toegediend □ vanaf OK □ start IC	□ continueren bij temp < 36,0 ^{0} C □ afbouwen /stoppen indien temp > 36,0^0 C (stijgende trend , HD en drainlekkage binnen criterium)	□ Sedatie afbouwen …….uur □ Sedatie gestopt … ……..uur
Patiënt klaagt over (onduidelijke) pijn op de borst ondanks toegediende pijn medicatie	□ volg acties bij zie ST-segment afwijkingen, **indien onvoldoende resultaat** : □ geef 50 mcq fentanyl i.v. □ herhaal 50 mcq fentanyl iv na 5 min. bij pijnscore > 4 □ blijft POB bestaan , overleg met arts □ nadere diagnostiek is noodzakelijk	
Pijnscore > 4 ondanks medicatie door: wondpijn	□ geef 50 mcq fentanyl i.v. □ herhaal 50 mcq fentanyl iv bij score > 4 **ondanks extra pijnbestrijding:** □ overleg arts om morfinedosis te verhogen □ overleg arts, nadere diagnostiek is noodzakelijk	□ □
Rass score + 1 tot + 4 (onrustig tot strijdlustig)	**binnen 2 uur op IC:** □ overleg met arts	□
Rass score -1 tot -5 (slaperig tot niet wekbaar)	**binnen 3 uur op IC** □ indien sedatie zie kopje "patiënt krijgt sedatie toegediend" **na 3 uur op IC en geen sedatie** □ overleg met arts	□ □

Variantie Temperatuur	actie	beleid arts, tijdstip en actie
Centrale temperatuur < 36 ^{0} C	□ overleg met arts over propofol toediening	□
Centrale temperatuur > 38,0 ^{o} C	□ overleg met arts	□
Δ temp > 7 ^{0} C	□ overleg arts	□

Variantie respiratoire status	actie	beleid arts, tijdstip en actie
Patiënt niet gedetubeerd < 6 uur omdat:		
□ Te slaperig (Rass >- 2)	□ sedatie stoppen , na 30 min. opnieuw beoordelen	
□ Detubatie vereisten niet gehaald	□ overleg met arts	□

Variantie resp. status NA detubatie	actie	beleid arts, tijdstip en actie
Saturatie < 94 %	□ bespreek eventuele oorzaak met patënt □ controleer zuurstof toediening □ sluit pijn, onrust en shunting (nicardipine) uit □ controleer luchtlekkage thoraxdrain □ stimuleer tot effectief ophoesten **Indien onvoldoende resultaat:** □ geef non-rebreathing masker of aquapack 100 % □ check SpO_2 bij opname op vorige afdeling (C -1) □ accepteer iom arts een lagere saturatie	Oorzaak: □ Afbouwen of stoppen nicardipine □ NPPV □ Re- intubatie Saturatie > ……..%

Figure 1: Continued

Ademfrequentie > 30 / minuut	□ **Saturatie < 94 % zie variantie bij sat. < 94 %** □ **Saturatie > 94 %:** ○ bespreek eventuele oorzaak met patiënt ○ sluit pijn, onrust en angst uit ○ luchtlekkage drain ? of onbekend overleg met arts	□
Ademfrequentie < 12 / minuut	□ **Saturatie < 94 %** ○ zie oorzaken bij sat. < 94 % ○ activeer patiënt □ **Saturatie > 94 %** ○ observeer patiënt, (CAVE toediening opiaten) □ **licht arts in bij apneus en/of AH freq. < 6 / min.**	□
Variantie Algemeen	**actie**	**beleid arts, tijdstip en actie**
Patiënt is misselijk	□ geef 4 mgr ondansetron i.v. □ bij onvoldoende resultaat overleg met arts	□ maagsonde inbrengen
Variantie Laboratoriumuitslagen	**actie**	**beleid arts, tijdstip en actie**
Hemoglobine < 5,0 mmol/l	□ alleen in combinatie ↓ HD parameters / Hb <5,0 mmol/l → 1 PC □ overleg met arts indien HD stabiel	□
Trombo's < 75 10^9 /l	□ overleg met arts	□
Glucose > 8.0 mmol /l	1e meting (bij opname) glucose > 8.0 mmol/l □ meting herhalen na 2 uur **Indien 2e meting of iedere andere glucosemeting nadien > 8.0 mmol/l :** □ start en volg glucoseregulatieprotocol	als de glucose niet afwijkend is wordt deze 6 uur na opname opnieuwe bepaald.
Kalium (K) < 3,7 mmol/l	□ start en volg kalium suppletie protocol	
Kalium (K) > 5,0 mmol/l	□ licht arts in	□
Magnesium (Mg) < 0,85 mmol/l	□ start magnesium suppletie protocol	als er suppletie wordt gestart wordt het Mg 6 uur na starten opnieuw bepaald
Fosfaat (P) < 0,75 mmol/l	□ start fosfaat suppletie protocol	als er suppletie wordt gestart wordt het fosfaaf 6 uur na het starten opnieuw bepaald
Troponine T > 400	□ troponine T bepalen à 6 uur (volgens schema) totdat het niet meer stijgt Bij eerst volgende bepaling troponine T , CK meeprikken	□

List of abbreviations

CP	Clinical Pathway
WAI	Work as imagined
WAD	Work as Done
ERAS	Enhanced Recovery After Surgery
P-A-R-cycle	Prepare-Act-Reflect- Cycle
LOS	Length of Stay
ICU	Intensive Care Unit
PACU	Post Anesthesia Care unit
Log EuroSCORE	patients' predicted risk of death and survival prior to cardiac surgery
EWS	Early Warning Score
CS	Cardiac Surgery
CABG	Coronary Arterial Bypass Graft
TEVAR	Thoracic Endovascular Aortic Repair
TAVI	Transcatheter Aortic Valve Implantation
PDMS	Patient Data Management System
APACHE	Acute Physiology and Chronic Health Evaluation Score
CORRAD	CORonary artery surgery database RADboudumc
NICE	National Intensive Care Evaluation
[IQR]	Interquartile range
SD	Standard deviation
SDD	Selective Decontamination of the Digestive Tract
$ScvO_2$	central venous oxygen saturation
MUST	malnutrition universal screening tool
TPN	Total Parenteral Nutrition
SMA	Superior Mesenteric Artery
OR	Operating Theatre
EBM	Evidence Based Medicine
EBP	Evidence Based Practice
KPi	Key Performance indicator

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Hettie Custers, je hebt met je intensive care achtergrond geleerd om naar het geheel van de processen rondom een operatie patiënt te kijken en daardoor heb je meerwaarde binnen de ontwikkeling en uitvoering van de paden voor hoog-risico chirurgie. Dank dat je als medicus binnen het operatiekamer–complex in de directe peri-operatieve zorg, onze gastro-intestinaal chirurgische patiënten op het juiste pad houdt. Het is altijd een veilig idee als jij aan tafel staat, op de achtergrond meekijkt of de scepter zwaait op de PACU.

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Rob Bleichrodt, je rol in mijn ontwikkeling is groter dan je waarschijnlijk zelf denkt. Je hebt me de kans gegeven om in het Radboudumc als eerste chirurg-intensivist in Nederland een baan als chirurg voor complexe abdominale chirurgie te combineren met een baan als intensivist. Een dubbelrol en soms een duivels dilemma. Je hebt laten zien "it always seems impossible untill it's done"(Nelson Mandela).

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Curriculum Vitae

Marion van der Kolk grew up in the village Ittersum close to the city of Zwolle. After graduating from the Thomas à Kempis Scholengemeenschap (Atheneum B) in Zwolle, she studied Medicine at the University of Groningen. She graduated "Cum Laude" from medical school.

After her internship at Medisch Spectrum Twente in Enschede, she became resident at the department of surgery at Medical Center Leeuwarden (Dr. P.L. de Vogel). She started her surgical residency at Maximà Medical Center in Veldhoven (Dr. C.M.A. Bruyninckx) and continued her surgical residency at Radboud University Medical Center (Prof.dr. R.J.A. Goris). After becoming a surgeon she continued her training as a fellow in gastro-intestinal surgery at the department of surgery at the Radboudumc. Her interest in intensive care medicine and peri-operative care arose in Leeuwarden and after her fellowship she became a CHIVO (Chirurg-in-vervolg-opleiding) in Intensive Care Medicine at the department of Intensive Care at Maastricht University Medical Center (Prof.dr. G. Ramsay) and Amsterdam Medical Center (Prof.dr. J. Kesecioglu). She obtained her European Exam in Intensive Care Medicine in Rome in 2000.

In 2001 she was appointed as a staff surgeon at the department of surgery and as a staff intensivist at the department of intensive care at the Radboudumc. She has been a member of the board of the Dutch Society of Intensive Care medicine (NVIC) and a member of the Gemeenschappelijke Intensivisten Commissie (GIC). She was a founder and a board member of the organization and instructor in Fundamentals in Critical Care Support Nederland (FCCS).

Member of the working group National Guideline CBO: Esophagealcarcinoma 2002-2004 and working group National Guideline CBO: Organization and structure Intensive Care 2002-2005. She was appointed chair of the committee Intensive Care and peri-operative care of the Dutch Society of Surgeons (NVvH) 2004-2012. Member Patient Safety Agency Programme (VWS) to develop a national guideline for early "recognition of the vitally threatened patient" and member of the team that developed and implemented the Early Warning Score and Medical Emergency Team at the Radboudumc together with the essential ALERT training.

Since 2012 she works as a colorectal and pancreas surgeon at the department of gastro-intestinal and oncologic surgery of the Radboudumc and has many functions associated with quality and safety. In December 2017 she was appointed by the Board of the Radboudumc as Chair and Clinical leader of the project: Care Pathways. Their mis-

sion is to redevelop and innovate Care Pathways into patient-centered care pathways within the Radboudumc and its Network.

Marion lives with her partner Robert Kraaijenzank, their daughter Veerle (2005) and their Labrador Retriever Luna (2016) in Doorwerth.